Journal of the

AMERICAN PHARMACEUTICAL ASSOCIATION

VOL. XIV, No. 8
CONSECUTIVE No. 15

Practical Pharmacy Edition

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AUGUST, 1953

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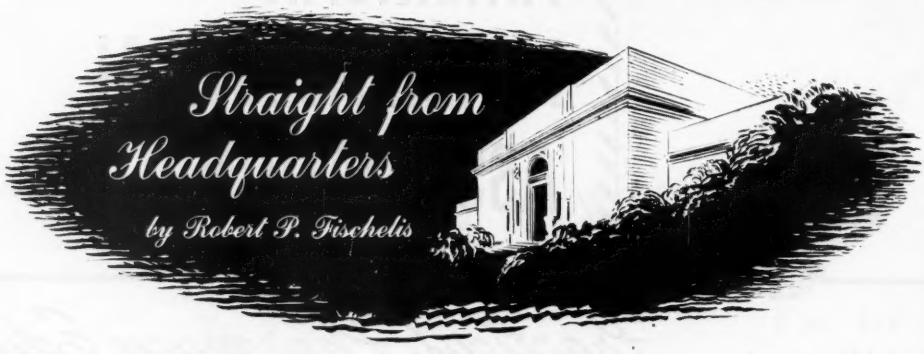


O.D.M. and Polio Foundation Give Assurance That Controlled Distribution of Gamma Globulin Is Temporary

WE STATED the position of the professional and public health minded pharmacists of the United States on this question in the April issue of THIS JOURNAL, beginning on page 213.

The following statement has been released by the Office of Defense Mobilization and is of special interest to the pharmacists of the United States:

The present plan of distribution of gamma globulin which is being coordinated by the Office of Defense Mobilization was developed to serve the over-all interests and needs of the American people. It was undertaken after extensive discussions with responsible individuals in the fields of medicine, public health, research, and industry.

More than 75 per cent of the expected supply of gamma globulin for 1953 will be produced from blood donated by the American people. In addition the processing costs of all gamma globulin being distributed in the program are being paid with funds donated by the American people to the American National Red Cross and the National Foundation for Infantile Paralysis. Thus, there is an obligation to return the blood derivative to the people in an equitable manner and by a method which will assure the most effective use of the limited supply.

Failure to provide such a method could deprive certain individuals and communities of needed protection while the required material was being held in other areas which had no such need.

The present distribution plan is designed for an emergency period only, until there is an adequate supply of gamma globulin which would enable distribution to be returned to normal channels.

Mr. Basil O'Connor, president of the National Foundation for Infantile Paralysis, has written us as follows:

It was only after reading the editorial "Whose Blood?" which appeared in the April issue of the *Journal* of the AMERICAN PHARMACEUTICAL ASSOCIATION, that I realized how deep an understanding individual pharmacists and the entire pharmaceutical profession had of the extraordinary problems which have developed because of the short supply of gamma globulin for poliomyelitis prophylaxis. It was a gratifying experience to have this proof of the basic philosophy which guides the members of your profession.

Perhaps it will be of further interest to your members to have me clarify the role the National Foundation for Infantile Paralysis played in the development of this unusual situation.

As part of a broad program of research which the National Foundation has supported to the extent of approximately twenty million dollars in the past fifteen years, the National Foundation gave its financial support to the scientific field trials during 1951 and 1952 which demonstrated the temporary protective effect of gamma globulin against paralytic poliomyelitis.

Once this major objective had been achieved, the National Foundation's second role was to attempt to augment the supply of gamma globulin which surveys indicated would be completely inadequate to meet the expected demand. The only possible source of supply remaining—since the American National Red Cross and the Armed Services had pledged their contributions to the national stockpile—was that of the commercial processors of gamma globulin derived from blood other than that collected by the Red Cross. After a series of conversations with representatives of the leading producers, these firms readily agreed to sell to the National Foundation their total production up to June, 1954.

Inasmuch as the Office of Defense Mobilization had been designated by the Government—since the outbreak of the Korean War—as the agency in

charge of blood and blood products as critical defense items, the National Foundation offered to turn over to that agency all the commercial gamma globulin it purchased to augment the national stockpile. Understandably, the offer was accepted.

These two major operations have been the extent of the National Foundation's role in the gamma globulin picture.

The distribution and allocation plans which were promulgated by the Office of Defense Mobilization on April 15 were formulated on the advice of special committees appointed by that agency. The National Foundation was not represented on any of those decision-making bodies.

Obviously, I cannot speak for the Office of Defense Mobilization. But I feel as you do, that this should not be regarded as a pattern for normal or future action but as an emergency action necessitated by the urgency of the situation. I am confident that the philosophy guiding the decision was an attempt to allocate an inadequate supply of a medicinal product on the basis of the medical needs of the public.

We believe that these two statements, one from the National Foundation for Infantile Paralysis and the other from The Health Resources Advisory Committee of the Office of Defense Mobilization, should set at rest any question that has been in the minds of those who have viewed with alarm the possibility of interference with the system of private enterprise that governs the distribution of drugs and medicines in the American way of providing proper medical care.

The recent programs of mass prophylaxis against poliomyelitis in Alabama and North Carolina offering hope to approximately 40,000 children in epidemic areas would not have been possible without a controlled distribution plan.

We have been informed that before allocation plans were put into effect, one well-meaning community had already negotiated to purchase about 3 per cent of the total commercial supply to serve one small community in a state. This is but one known example of planning to purchase through legitimate channels that would result in depriving many other people of a product that may or may not have been needed in that community this season.

The initial mass inoculations with gamma globulin and the results thus far achieved are the best evidence that distribution of this life and health preserving procedure should have been handled as it is being handled.

Pharmacies Are Not Factories

THE Senate of the United States almost became the victim of the continued efforts of those who tried to put over the idea that pharmacies are factories in the eyes of the law, when it comes to the inspection authority of the Food and Drug Administration. The last-minute efforts to undo the good work that had been done on the floor of the House in the debate on H.R. 5740—the factory inspection amendment to the Food, Drug, and Cosmetic Act—almost succeeded.

Without conducting any hearings on H.R. 5740 after it reached the Senate, the Committee on Labor and Public Welfare referred the bill to a subcommittee which prepared an amendment to Section 503 (b) of the present Food, Drug and Cosmetic Act to be known as paragraph (6), and which read as follows:

"Prescription files in retail drug stores may be inspected only in accordance with the procedure prescribed in Section 704 as amended, and only when the officer or employee giving notice of inspection

"(a) has reason to believe that the retail drug store has dispensed drugs in violation of this Section; or

"(b) is engaged in tracing the distribution of a dangerously adulterated or misbranded drug or a new drug for which there is no effective application under Section 505."

Obviously paragraph (a) above completely nullified the intent of the House of Representatives as expressed on the floor of the House, and there is little doubt as to who suggested this amendment to the busy Senators who were occupied with such important matters as the immigration bill, the extension of the debt limit, and other last-minute "must" legislation. The full committee agreed to the amendment, and then the bill was brought to the floor of the Senate on the final day of the present session, where it was passed with a change in paragraph (a) above, substituting the word "evidence" for the words "reason to believe."

However, when the amended Senate bill reached the House for concurrence, there was immediate objection to the Senate amendment and the House stood by its original bill and rejected the Senate amendment. The Senate then passed H.R. 5740 exactly as it was originally passed in the

(Continued on page 488)

Straight from Headquarters

• • • • • • • • • *from preceding page*

House, thus ending the maneuver to reverse the intent of Congress with respect to retail pharmacy inspections.

As this is written, the bill is on its way to the President, who will undoubtedly sign it since he mentioned the need for factory inspection in his State of the Union Message.

It is important to note that the President said nothing in his message about inspection of retail pharmacies; that the debate on the floor of the House, which is the only place where the issue was really considered on its merits, clearly set forth that retail pharmacies were not to be included in the provision for factory inspection. The report written hurriedly for the Senate Committee in support of H.R. 5740 and its committee amendment could hardly have been given much consideration by the members of the Senate when they originally voted on the amended bill.

To anyone who reads this committee report, it must be clear that the same people who wrote the report which the full Committee on Interstate and Foreign Commerce of the House of Representatives rejected, placed the discredited portion of the House report into the Senate report.

It is well that the members of the House of Representatives were alert to what was going on and rejected the product of these machinations and the attempt to nullify their clear intentions.

At Salt Lake City

WHILE pharmacists throughout the United States are reading this issue of the JOURNAL, more than 1,000 members of the AMERICAN PHARMACEUTICAL ASSOCIATION are assembled in convention at Salt Lake City, Utah.

The House of Delegates will be well attended by every organization entitled to membership. Some of the topics which will come up for discussion and action as the result of the reports of officers and committees include: the distribution of scarce drugs such as gamma globulin; legislation dealing with regulation of the production and distribution of drugs at federal and state levels; the pharmacist's changing function in the healing arts and problems growing out of the multiplication and nomenclature of drugs; the development of official compendia on a national and international scale; inter-professional relations; public relations; organization of the AMERICAN PHARMACEUTICAL ASSOCIATION FOUNDATION; economics of prescription practice; a national pharmacy examination; change in time of A.PH.A. meetings; National Pharmacy Week; professional manpower problems in pharmacy; civil defense, and military pharmacy. Those who are not at the convention may have an opportunity on Wednesday, August 19, at 10:00 p.m., E.D.T., to listen to a broadcast entitled "Under the Sign of Jupiter" emanating from the National Broadcasting Company and prepared in cooperation with Smith, Kline & French Laboratories of Philadelphia.

This broadcast will salute the modern pharmacist in a special half-hour dramatic program that will be heard from coast to coast.

When this Convention adjourns, we are sure that it will have laid the groundwork for greater professional activity in behalf of the pharmacists of America. Our September issue will report the meeting in detail.

Dentists Criticize Toothpaste Claims

THE *Journal of the American Dental Association*, in an editorial in its July issue, declared that the "increasingly exaggerated" claims made for toothpastes and powders have produced growing concern among members of the dental profession.

The *Journal* said advertisers were riding "roughshod over the public" in the face of all scientific evidence to the contrary.

"Many of these superclaims are on the same low level as those made for discredited cancer cures and arthritis remedies," the editorial states.

The American Dental Association's Council on Dental Therapeutics, which evaluates dental products, has not recognized the claims of special curative qualities for any dentifrice now on the market on the grounds that inadequate evidence exists to substantiate such claims.

The Council has reported that no dentifrice offered to the public has been shown to have a usefulness beyond assisting the toothbrush in cleaning the accessible surface of the teeth.

NATIONAL PHARMACY WEEK DISPLAY CONTEST

1852 APhA 1953
SECOND CENTURY

Prizes

1	$200
2	$100
3	$50

OCTOBER 4-10, 1953

NATIONAL PHARMACY WEEK WINDOW-DISPLAY CONTEST

An Invitation to the Pharmacists of America to Participate in the Observation of National Pharmacy Week, October 4 through October 10, 1953

DURING the last several years, National Pharmacy Week has acquired a new significance. It has been dedicated by the pharmacists of America to the advancement of medical care. The American drug store has been featured as a source of health information. Window displays have been prominent in the observation. Year by year, more and more pharmacists participate. This year, pharmacists are invited to exercise individual initiative in the development and design of displays for National Pharmacy Week, using as a theme the slogan

YOUR PHARMACIST WORKS FOR BETTER COMMUNITY HEALTH

Here is an opportunity for the practical application of creative imagination in directing attention to your drug store as the health center of its community. Please install your window display, have it photographed, and send a glossy print as soon as possible to the committee designated in the rules which follow.

RULES FOR NATIONAL PHARMACY WEEK DISPLAY COMPETITION

GENERAL

1. Competition is limited to members of the AMERICAN PHARMACEUTICAL ASSOCIATION. In instances where a photograph is entered in the name of a retail pharmacy rather than by an individual, a member of the AMERICAN PHARMACEUTICAL ASSOCIATION must be associated with the firm, either as an owner or as an employee, and must have had a part in the planning of the display.
2. Each display must exhibit the window strip entitled "National Pharmacy Week, October 4–10, 1953," which the AMERICAN PHARMACEUTICAL ASSOCIATION will supply.
3. Displays will be judged on the basis of:
   (a) Value and effectiveness of the message to the public
   (b) Originality
   (c) Professional character, arrangement, and details
   (d) Conformity to theme
4. Displays must be entirely professional in their concept. Any emphasis on commercial implications must be avoided.
5. Photographs submitted must be 8- by 10-inch glossy prints.
6. Pharmacy Week displays that have been entered in former years are ineligible.

Every pharmacy in the country will receive this National Pharmacy Week Window streamer, measuring 44 x 6 inches, in a special mailing late this month

RETAIL PHARMACIES

1. General Rules 1 to 6, inclusive, apply to this competition, which is limited to displays in retail pharmacies.
2. Photographs of displays must be submitted to the secretaries of the respective state pharmaceutical associations on or before November 15, 1953, labeled on the back as entries in the Retail Pharmacy Competition.
3. Each state pharmaceutical association should appoint a judging committee before November 15, 1953, to select the best display within the state. A photograph of that display shall be mailed to the AMERICAN PHARMACEUTICAL ASSOCIATION, 2215 Constitution Avenue, N. W., Washington 7, D. C., not later than December 15, 1953. Entries mailed after that date will not be accepted in the national competition.
4. Only the winner from each state may be entered in the national competition.
5. As soon as possible after December 15, 1953, a national committee of judges will select the best six displays from the states. The winning displays will be awarded the following:
   1. $200 and plaque or other trophy
   2. $100 and plaque or other trophy
   3. $50 and plaque or other trophy
   4. } Certificates of merit
   5. }
   6. }

PUBLIC EXHIBITS

1. General Rules 1 to 6, inclusive, apply to this competition.
2. Displays or exhibits in the Public Exhibit Competition must be installed in a public place other than a retail pharmacy, pharmacy college, or hospital. One entry may be submitted by any pharmacist or group of pharmacists, including hospital and retail pharmacists, state and local associations, schools of pharmacy, and local branches of the AMERICAN PHARMACEUTICAL ASSOCIATION.
3. Photographs of displays shall be mailed to the AMERICAN PHARMACEUTICAL ASSOCIATION, 2215 Constitution Avenue, N. W., Washington 7, D. C., on or before December 15, 1953. Entries mailed after that date will not be accepted in the competition.
4. As soon as possible after December 15, 1953, a national committee of judges will select the best three public exhibit entries. The best display in this group will receive the AMERICAN PHARMACEUTICAL ASSOCIATION Award, which shall be a suitable trophy, and the others will receive certificates of merit.

PHARMACY COLLEGES

1. General Rules 1 to 6, inclusive, apply to the Pharmacy College Competition, which is limited to displays or exhibits planned and installed by pharmacy students at their college or other public place.
2. Only one photograph from each college may be entered.
3. Photographs of displays shall be mailed to the AMERICAN PHARMACEUTICAL ASSOCIATION, 2215 Constitution Avenue, N. W., Washington 7, D. C., on or before December 15, 1953. Entries mailed after that date will not be accepted in the competition.
4. As soon as possible after December 15, 1953, a national committee of judges will select the best three displays from the colleges. The best display in this group will receive the AMERICAN PHARMACEUTICAL ASSOCIATION Award, which shall be a suitable trophy, and the others will receive certificates of merit.

HOSPITALS AND CLINICS

1. General Rules 1 to 6, inclusive, apply to the Hospitals and Clinics Competition, which is limited to displays or exhibits planned and installed in hospital or clinic lobbies or other hospital or clinic areas open to the general public.
2. The entry must be submitted in the name of the hospital or clinic by the hospital administrator and chief pharmacist jointly.
3. Only one photograph from each hospital or clinic may be entered.
4. Photographs of displays must be mailed to the AMERICAN PHARMACEUTICAL ASSOCIATION, 2215 Constitution Avenue, N. W., Washington 7, D. C., on or before December 15, 1953. Entries mailed after that date will not be accepted in the competition.
5. As soon as possible after December 15, 1953, a national committee of judges will meet to select the best three exhibits in this group. The best exhibit will receive a plaque suitable for hanging in a prominent place in the hospital or clinic, and the other two will receive certificates of merit.

★ Special Kit Prepared for ★

PHARMACY WEEK OBSERVANCE

Committee on Public Relations of the A.Ph.A. has prepared a special promotion kit, containing addresses, radio and television interviews, programs and announcements; as well as newspaper releases, editorials, and other material.

THE Committee on Public Relations of the AMERICAN PHARMACEUTICAL ASSOCIATION has completed a special promotion kit for National Pharmacy Week, and it is now available to pharmacists for the nominal charge of $1.00. In all, the material covers every type of media, from newspapers to window displays. Seven addresses are also included, for delivery before service clubs, youth groups, and other organizations. An advertising mat goes with each kit.

Pharmacists should order their kit from the Committee on Public Relations, AMERICAN PHARMACEUTICAL ASSOCIATION, 2215 Constitution Avenue, N.W., Washington 7, D.C.

WELL-ROUNDED PROGRAM

In preparing material for this year's observance, the Committee has attempted to help the pharmacist as much as possible by including press releases and other related material. For example, a special press release has been prepared to cover the major points in the addresses and radio interviews, so that the speaker need only fill in his own name and address and submit the release to his local paper. Where possible, participants in National Pharmacy Week are urged to re-type these releases, submitting one to each of their community's newspapers. A pre-release also accompanies each address and interview, so that the speaker can advise the newspapers of the proposed address, thus getting newspaper coverage before and after the talk.

Three suggested editorials are included in the kit, along with a fact sheet on pharmacy from which editors can select statistics on which to build an editorial of their own. With this material, as well as with all other material in the kit, an instruction sheet is provided to guide the pharmacist in how he can get the most out of it. Bert Mull, Chairman of the Public Relations Committee, has written a special introductory message for the kit explaining its organization and content, in which he points out that these instruction sheets are merely included to help local National Pharmacy Week participants in their promotional program. "We are not telling people how to run their own observance," Mr. Mull stated. "Instead, we are merely trying to point out to these pharmacists ways and means that they can use to increase their local press coverage of National Pharmacy Week. By including these instruction guides we are trying to encourage the highest possible local support, for it is through such local support that the practicing pharmacist gains the most."

RADIO AND TV MATERIAL

For the first time, the National Pharmacy Week Committee has prepared special material for use on television. The suggestions contained in the kit are the result of conferences with television writers and producers, and pharmacists who have appeared on local television programs. Several examples of simple demonstrations are given, to add interest to the television interview.

Two fact sheets accompany each radio interview. The first is a brief summation of the major points made in the interview, so that the announcer can have a better understanding of the subject matter. The second is a fact sheet on the pharmacist being interviewed, on which he will fill in name, address, years in the community, and other information. The announcer will then have, at his finger tips, all pertinent facts, and the result will be a more informal interview.

Two dramatic presentations for radio are also

included. One, the script for the highly successful fifteen-minute play, *The Prescription that Shook the World* should be offered to a local radio station for broadcast sometime during National Pharmacy Week. Additional copies of this script will be made available to stations requesting them, according to Mr. Mull. The second radio program is an outline of a musical presentation, requiring standard music from the station recording library. The text points up the professional and community service of the pharmacist.

KIT CAN BE USED AT OTHER TIMES

"The kit," Mr. Mull said recently, "is essentially designed for observance of National Pharmacy Week. However, we of the Public Relations Committee recognize that good public relations is a continuing thing, and for that reason, we have included considerable material in the kit this year that can be used after National Pharmacy Week. We urge all pharmacists to keep their kit, and use it, from time to time, during the months ahead." Mr. Mull singled out several of the addresses and radio interviews as examples of material that can be used at any time during the year.

Pharmacists are urged to order their kits early, since the supply is limited.

THIS IS WHAT THE NATIONAL PHARMACY WEEK KIT CONTAINS

Addresses:

1. American Pharmacy and the American Pharmaceutical Association (a 20-minute address reviewing the progress of American pharmacy over the last century)
2. Behind the Scenes in Your Corner Pharmacy (a 15-minute address reviewing ethical and legal controls in the practice of pharmacy)
3. The Pharmacist—Then and Now (a 15-minute address on the historical background of pharmacy)
4. Pharmacy—a Modern Career in the Health Field (a 15-minute address for delivery before high school students)
5. Famous Discoveries by Famous Pharmacists (a 10-minute address on pharmacy's contribution to science)
6. The Pharmacist's Show Globe (a 15-minute review of the legends connected with the Show Globe)
7. Pharmacy Through the Ages (a 15-minute historical review of pharmacy from ancient days to the present)

Radio & TV:

8. The Start of the Second Century of Organized Pharmacy in America (a 3-minute radio address)
9. Your Pharmacist (a 3-minute radio address)
10. Modern Pharmacy (a 5-minute interview on the current practice of pharmacy)
11. Knowing the Facts Saves Lives (a 5-minute interview on the importance of early diagnosis)
12. The Cost of Medical Care (a 5-minute interview pointing out that while medicine may seem costly, patients are returned to work faster)
13. A Visit with Your Pharmacist (a 5-minute interview discussing the pharmacist's role in the storing, handling, and dispensing of modern medication)
14. The Search for New Drugs (a 13½-minute interview on the discovery and development of a new drug)
15. New Drugs in the Pharmacy (a 13½-minute interview requiring an announcer and two pharmacists)
16. Your American Pharmacist—in Words and Music (a script for a half-hour program, covering the pharmacist in American society)
17. The Prescription That Shook the World (a script for a 15-minute dramatic presentation based on Klaproth's discovery of uranium)
18. Spot Announcements (a variety of 15, 30, and 45-second announcements for use during National Pharmacy Week)
19. The Practice of Pharmacy (outline of a television interview)
20. Television Demonstrations (a list of demonstrations that have proved successful on television)

Newspaper and Miscellaneous Material

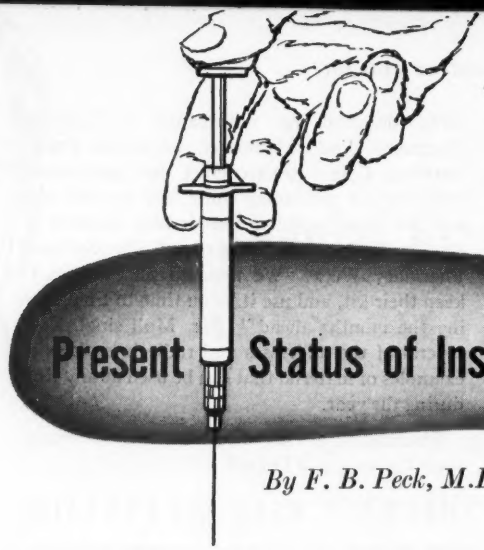
21. Editorial Material (two suggested editorials which the paper may use, plus a fact sheet on pharmacy from which the editor can get material for an original editorial)
22. Governor's Proclamation
23. Mayor's Proclamation
24. A newspaper mat
25. Suggestions for your National Pharmacy Week Window Display

Twenty-five sample press releases are included in the kit, covering the material in each of the addresses and radio interviews.

ORDER YOUR KIT TODAY.

Send $1.00 to:

Committee on Public Relations
American Pharmaceutical Association, 2215 Constitution Avenue, N.W., Washington 7, D.C.



Dr. Peck reviews the development of insulin modifications since 1936

Present Status of Insulin Modifications

By F. B. Peck, M.D.†

SINCE the discovery of protamine insulin by Hagedorn and its introduction into clinical usage in 1936, there has been a constant stream of modifications of insulin having the common attribute of prolonged action by virtue of differences in solubility in tissue fluids at the approximate pH of the body. In general, such modifications have been prepared according to the original principles laid down by Hagedorn, utilizing combinations of insulin with protein precipitants described by him (protamines, histones, globins, kyrins) or by means of chemicals (hexamine, isocyanate, polyvinylpyrroladone) capable of altering solubility. The physical characteristics of such preparations vary from clear to cloudy suspensions, depending upon the occurrence of precipitation at various pH ranges. By varying the quantity of the agent used in proportion to the insulin, and the zinc content, or both, either in bulk or extemporaneously by mixing, the preparation of a wide variety of combinations having time activities ranging between the short, profound action of regular insulin and the long, slow effect of protamine zinc insulin is made possible.

All these preparations display the characteristic hypoglycemic action of insulin, but they differ from one another in rate of onset of action and duration of effect. Thus far, duration of action has never been obtained except at the expense of rapidity of onset. The selection of a given preparation for wide-scale use has, consequently, necessitated long-term and laborious clinical comparisons to establish the value of any specific time activity. Clinically the major problem has been to determine which particular time activity best meets the average daily needs of the greatest number of diabetic patients.

Clinical Reports

The progress of these studies has been reviewed from time to time during the last decade. More than a score of so-called intermediate acting preparations have been tested. They exert their greatest usefulness and display their most critical differences in timing in severe (unstable) cases of diabetes, and their differences tend to be minimized and become unimportant in stable or mild cases. That controversial evidence of clinical differences in timing between globin insulin with zinc and NPH insulin exists is doubtless the result of choice and number of cases subjected to critical analysis. The statistical data compiled by Izzo seems incontestable in this connection and, furthermore, the clinical impressions of longer duration of action of NPH insulin have been borne out by the Toronto assay curves published by Jamieson, Lacey, and Fisher.

The most generally useful of these preparations have been those which have acted in the range exhibited by 2:1 admixtures of insulin and protamine zinc insulin. Many clinical reports substantiate the essential similarity of action of NPH insulin to 2:1 mixture. Since the clinical usage of NPH insulin has been widely broadened by its introduction on the market in 1950, further review of this more recent experience is presented at this time. The entire bibliography on this subject is far too large to include in toto, so for earlier references the reader should refer to the reviews already cited.

A number of recent reports on the comparative effectiveness of NPH insulin have appeared in the literature. Baganz and associates studied 41 patients hospitalized on a metabolic service. All had been standardized on insulin in one form or another before each case was transferred to a single dose of NPH insulin before breakfast. It was found that the postprandial effects of NPH insulin were superior in all cases that had previously received only protamine zinc insulin and were as good in almost all cases previously receiving protamine zinc insulin and unmodified insulin.

Sharkey and King reported an experience gained from 18 months' observation of 28 diabetic patients both in the hospital and in office practice. Sixteen cases were treated satisfactorily with NPH insulin alone, and the remaining 12 required NPH insulin and unmodified insulin in a mixture. Insulin reactions were reduced in severity and over-all control was improved.

Edwards, Vance, and Mulholland made comparisons of 2:1 mixture, NPH insulin, and globin insulin with zinc in 21 cases. Their findings bore out the observation that all three modifications can be used satisfactorily in the mild and moderate diabetic, but in the more severe or complicated case the

† Director, Medical Division, Eli Lilly & Co.; Assoc. Prof. of Medicine, Indiana University School of Medicine; Consultant, Dept. of Medicine, Indianapolis General Hospital.

"carry-over" effect of NPH insulin or the 2:1 mixture was found to be highly desirable.

Dolger described a broad experience covering 185 severe diabetic patients observed for extended periods. Seventy-two of his group were satisfactorily controlled with NPH insulin alone. The remainder required mixtures in varying proportions. The author commented that NPH insulin will provide adequate coverage for 40 per cent of the patients with severe diabetes mellitus and is also suitable for patients whose insulin requirements are low or moderate.

Groff, Engelhardt, and Skelton studied 17 hospitalized diabetic patients who had been selected because their cases were moderately severe or severe, and they were free of discernible complicating factors. They found the improvement in control of diabetes in this group to be particularly valuable and noted remarkably uniform activity of the preparation during the 24 hours.

Greenhouse, drawing on four years' experience with various modifications of insulin, pointed out that NPH insulin has other advantages over and above improved timing characteristics. Insulin reactions tend to be less insidious than those resulting from protamine zinc insulin and, therefore, easier to recognize and treat. Furthermore, local allergic reactions tend to be diminished when NPH insulin is used. Palmer and others also reported a lowered incidence of insulin reactions in 28 patients observed over a two-year period.

Swallow and Chute obtained as good or better control with a single injection of NPH insulin as obtained with double injection of unmodified insulin and protamine zinc insulin in 10 out of 18 children. Two of the cases, both under 6 years, were noteworthy in that daytime hyperglycemia was associated with nocturnal hypoglycemia.

Shuman and Francis indicated that NPH insulin was effective in controlling both the fasting and the post-prandial glucose levels in the majority of 33 patients studied, despite both medical and surgical complications.

Other published reports mention the utility of NPH insulin in a wide spectrum of the diabetic population resulting in satisfactory control with a minimum of inconvenience to the patient.

Expanded Clinical Trial

There are several phases involved in the investigation of any new therapeutic agent which have been successively undertaken in studies of NPH insulin. After determination of its time activity in intensive but small-scale comparisons, the new preparation was applied on a larger scale in hospital wards and in outpatient groups. As a final step, when supplies became available, experimentation was extended and more and more investigators began to test the preparation under conditions of actual wide-scale practice until several thousand cases were under treatment. Reports of this experience were accumulated; 1,281 cases were in sufficient detail to permit analysis. It was anticipated that this study would be heavily weighted with problem cases not previously controlled satisfactorily. Of the 1,281 cases, 522 were classified as severe, brittle, or juvenile, 562 as moderate, and only 197 as mild. Furthermore, in age distribution, one-third of the group was under 30 years of age. Practically all patients in these studies were diabetics whose "pedigrees" were well known to the investigators, and it can be assumed that the therapy used prior to NPH insulin controlled the disease as well as possible and had shown the best results in each case.

The types of insulin therapy before NPH insulin was utilized were those known and in use. Of all patients, 89.5 per cent were taking protamine zinc insulin in one form or another, with the insulin mixtures accounting for almost one-half of the entire group.

Of much interest are the data relative to the degree of diabetic control achieved in the comparative study. In all three groups—classified mild, moderate, or severe—there was a significant shift toward better management when NPH insulin was used. This shift applied not only to the severe group, where it was anticipated that more efficient timing of insulin effect would result in improvement, but also most markedly to the mild group where Izzo has shown that timing characteristics of insulin are least critical. In the mild group, "excellent" control was obtained in 39 per cent of the cases on prior insulin therapy, and this figure rose to 65 per cent following treatment with NPH insulin. Cases previously classified as having "poor" control diminished to 1.7 per cent.

Results in the "severe" group, both before and after NPH insulin, tend to emphasize the limitations of any insulin preparation used, since obviously no one insulin preparation as yet available is capable of controlling satisfactorily all cases of diabetes. Nevertheless, the data do show that improved control resulted when NPH insulin was used. Stephens, Donaldson, and Marble have shown that the employment of supplements of unmodified insulin, either as separate injections or mixed with NPH insulin, provides better results, particularly in the juvenile patients. The possibility of employing such a mixture had been previously suggested by Sprague, and by Shuman and Francis.

The incidence of insulin reactions was also of interest, and investigators were asked to enumerate the number and time of occurrence of reactions in the cases they observed. Over one-half reported a lessening in number of reactions, and an additional 23 per cent indicated that there had been no reactions at all when NPH insulin was used.

There was a lack of uniformity as to time of day that reactions were observed. This is surprising, since protamine zinc insulin is more prone to cause reactions in the early morning hours and globin insulin with zinc has a tendency to exhibit its peak effect manifested by hypoglycemia in the middle to late afternoon hours. Of those patients who had reactions while using NPH insulin, 34.5 per cent experienced them in the morning, 37.7 per cent reported afternoon reactions, and 27.18 per cent had them in the evening. These figures seem to indicate that hypoglycemia reactions with NPH insulin follow individual variations in the patient's response to insulin, modified by diet and exercise. A similar lack of pattern in time of hypoglycemia was noted

(Continued on page 520)

A Census of Pharmacy 1948-1953

A comparison of the figures released by the National Association of Boards of Pharmacy for the years 1948 and 1953 reveals considerable information on professional and employment trends in pharmacy in the United States over the past five years.

NO. OF PHARMACIES IN THE UNITED STATES

NO. OF PHARMACISTS, REGISTERED, ENGAGED IN PRACTICE

January 1, 1948	50,05
January 1, 1953	53,66

NO. OF REGISTERED PHARMACISTS ENGAGED IN PRACTICE IN

	Retail
January 1, 1948	79,910
January 1, 1953	94,475

STATUS OF PHARMACISTS: OWNERSHIP VS. EMPLOYEE

January 1, 1948	52
January 1, 1953	56

AGES OF PHARMACISTS

	Under 30	30-	40-49
January 1, 1948	9.0%	23.0	2.0%
January 1, 1953	16.0%	21.	9.0%

EDUCATIONAL QUALIFICATIONS

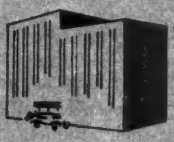
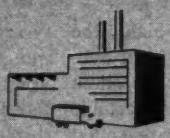
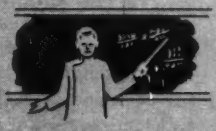
	Graduates 4 yr. cours	3 yr. co
January 1, 1948	29.0%	16.0
January 1, 1953	46.6	

Statistics for 1948 include an estimated 3,000 pharmacies in Illinois, only state not reporting actual total; figures include 1,221 hospital pharmacies in 43 states in 1948 and an estimated 2,000 hospital pharmacies in all states in 1953.

* Figure for 1948 includes registered pharmacists in Illinois, estimated at 5,000.

93,753*

104,966

	Retail	Hospital		Manu. & Distribution		Teaching & Gov.	
							
	88.0	2,408	2.56%	5,073	6.3%	1,297	1.4%
	89.2	3,121	3.3%	5,087	5.4%	2,074	2.0%

1948 figures do not include Illinois pharmacists.

	Owners	Employees
	52.5%	47.5%
	56.0%	44.0%

1948 figures based on reports from 30 states with 48,280 pharmacists.

1953 figures based on reports from 40 states with 64,947 pharmacists.

	30	30–39	40–49	50–59	60–64	65–69	70
	23.0%		32.0%	20.0%	7.0%	5.0%	4.0%
	21.0%		29.0%	19.0%	7.0%	5.0%	3.0%

1948 figures based on reports from 24 states with 49,475 pharmacists.

1953 figures based on reports from 33 states with 67,877 pharmacists.

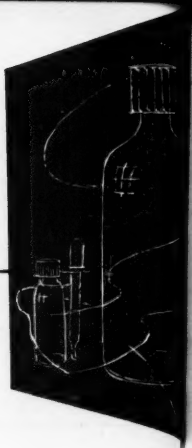
	Graduates 4 yr. course	3 yr. course	2 yr. course	non-graduate
	29.0%	16.0%	30.0%	25.0%
	46.6%	11.0%	22.7%	18.8%

1948 figures based on reports from 20 states with 21,957 pharmacists.

1953 figures based on reports from 29 states with 42,050 pharmacists.

ANTIBACTERIAL AGENTS

IN COMPOUNDED OPHTHALMIC SOLUTIONS



BY SAMUEL W. GOLDSTEIN

Director A.Ph.A. Laboratory

MUCH has been said and written about the preparation of isotonic and buffered ophthalmic solutions. Buffers added to obtain a pH at which a medicinal agent is more stable for a long period of shelf life are valuable and often necessary ingredients in manufactured ophthalmic solutions (1, 2). Some opinions indicate the possibility that in many instances the important result of an added buffer is the enhanced scientific appeal that can be made for the products, and that the buffer capacity of the lacrimal secretions can exert a sufficiently corrective activity in most cases (3–6). The clinical experience of Swan (4) leads him to question the need for making ophthalmic solutions isotonic with tissue fluids, unless the solution is to be instilled repeatedly or used for irrigation. He states: "The addition of non-medicament solutes to make ordinary eye drops isotonic is, therefore, unnecessary and increases the danger of the pharmacist's making an error in preparation of the prescription."

While there are differences of opinion about the essential need for making all ophthalmic solutions isotonic, and about the therapeutic or patient-acceptance value of buffered compounded solutions; very few individuals will disagree with the opinion that the control of bacterial and fungal growth in these solutions is desirable (7). Even when the contaminating microorganism is non-pathogenic, it might alter the medicinal agent or produce irritant substances. The danger of contamination with pathogenic microorganisms is present at the time of compounding, but the danger is very great when the solution is self-administered by the patient or when it is handled by persons who touch the applicator or dropper to the infected part and return it without sterilization to the container.

Federal Regulation

Reputable pharmaceutical manufacturers for years have scrupulously utilized accepted aseptic procedures in the preparation of marketed ophthalmic solutions and, for some time, many have taken the added precaution of adding a bacteriostatic agent to their products. In spite of the accepted precautions, several commercial lots of ophthalmic solutions were found to be contaminated. Theodore and Minsky (8), in December, 1951, cited the recall of solutions of a sulfonamide and of cortisone that were contaminated with *Pseudomonas aeruginosa* (*B. pyocyaneus*), and attention was directed to the absence of legal requirements for sterility of ophthalmic preparations in the United States. Accidental contamination of one batch of a commercial solution can mean that many bottles of the product will contain the contaminant, and the time lag between manufacture and sale for use will permit growth of bacteria in suitable media. The time factor is the only one that favors the extemporaneously compounded ophthalmic solution. There are certainly more probabilities for the contamination of compounded solutions.

The Food and Drug Administration, in the *Federal Register* of January 15, 1953, published the following regulation:

TITLE 21—FOOD AND DRUGS

Chapter 1—Food and Drug Administration, Federal Security Agency

Part 3—Statements of General Policy or Interpretation

Notice to Manufacturers and Repackers of Ophthalmic Solutions

Pursuant to section 3 of the Administrative Procedure Act (60 Stat. 237, 238; 5 U.S.C. 1002), the following statement of policy is issued:

3.28 Notice to manufacturers and repackers of ophthalmic solutions.

(a) Investigations by pharmaceutical manufacturers, physicians, and the Food and Drug Administration have revealed that liquid preparations for ophthalmic use contaminated with

microorganisms have been responsible for serious eye injuries and, in some cases, complete loss of vision. The Food and Drug Administration has conducted a survey of medical opinion and has found that it is the consensus of informed persons that such preparations should be sterile. It is evident that liquid preparations offered or intended for ophthalmic use purport to be of such purity and quality as to be suitable for safe use in the eye. The Federal Security Agency concludes that such preparations fall below their professed standard of purity or quality and may be unsafe for use if they are not sterile. Accordingly, liquid preparations offered or intended for ophthalmic use which are not sterile may be regarded as adulterated within the meaning of section 501 (c) of the Federal Food, Drug and Cosmetic Act and, further, may be misbranded within the meaning of section 502 (j) of the act.

(b) Liquid ophthalmic preparations packed in multiple-dose containers should (1) contain one or more suitable and harmless substances that will prevent the growth of microorganisms, or should (2) be so packaged as to volume and type of container and so labeled as to duration of use and necessary warnings as will afford adequate protection and minimize the hazard of injury resulting from contamination during use.

(Sec. 701, 52 Stat. 1055; 21 U.S.C. 371. Interprets or applies secs. 501, 502, 52 Stat. 1049, 1050; 21 U.S.C. 351, 352.)

Dated: January 12, 1953

(Seal) Rufus E. Miles, Jr.
Acting Administrator

F.R. Doc. 53-478; Filed, Jan. 15, 1953; 8:49 a.m.)

Extemporaneous Compounding

It is not difficult to believe that those who would interpret the "factory" inspection authority under the Federal Food, Drug and Cosmetic Law to include inspection of retail pharmacies in order to enforce the Durham-Humphrey amendment, would also include the retail pharmacy in the scope of this regulation.

Of more immediate importance to the pharmacist is his professional function to protect the public health to the best of his knowledge and ability. His latent knowledge of the possibility of dangerous contamination of ophthalmic solutions with microorganisms has been jolted into keen awareness of the situation. It remains to be seen how much of his ability he can and will apply to the problem.

Most pharmacists will agree that the ideal condition to insure sterility would find each pharmacy equipped to prepare and dispense sterile solutions in single-dose containers. A less desirable condition would have prescriptions for sterile extemporaneous products referred to pharmacies equipped to fill them. There is no immediate prospect that either of these conditions will be forced upon all pharmacies. Relatively few physicians are acutely aware of the need for specifying sterility for their prescribed eye washes and solutions. State Boards of Pharmacy know too well that it would be physically difficult for many small pharmacies to allot the necessary space for aseptic methods, even when a compact chamber is available. However, if pharmacy is to claim the right to be partially self-policed, it should not wait until a federal agency decides that it has the authority to enforce certain conditions in the practice of the profession before instituting at least an educational program to advance a desirable change.

A procedure for the preparation of small amounts of bacteria-free solutions has been described by Theodore and Feinstein (9). They utilize heat-sterilized equipment and bottles, a sterile solution of a chemical preservative as a vehicle, and filtration of the compounded solution through a Selas porcelain candle into a flask from which it is transferred to the dispensed container. All filtrations and transfers are made directly under a Sterilamp. A similar procedure, with the prepared solution filtered directly into a sterile dropper bottle under a bell jar, is being promoted to the pharmacists of Wisconsin. The necessary equipment for a sterile compounding chamber or cabinet was described at the Wisconsin Pharmacists' Institute, October, 1952 (10), and details of the so-called "Steri-Rx-Chamber" are available (11). It is hoped that such procedures will eventually become accepted practice.

There are several points that can be stressed in the educational phase which might prepare the way for the general acceptance by some pharmacists of the need for aseptic precautions in compounding ophthalmic solutions. We will assume that all pharmacists use distilled water to compound ophthalmic solutions. Distilled water that is transferred to a pint stock bottle that has not been sterilized is frequently contaminated with microorganisms. These contaminants usually are not pathogenic bacteria or molds, but frequent cleaning or sterilizing is a safe precaution. Recently boiled distilled water in which an antibacterial agent is dissolved can be used as a stock solution for ophthalmic prescriptions. The physician's consent to this practice must be obtained. A scrupulously clean compounding area directly under a sterilizing lamp could be the space now used for compounding. Inclusion of the number of individually wrapped, sterile plastic droppers in the dis-

(Continued on next page)

Antibacterial Agents

• • • • • *from preceding page*

pensed package to provide the prescribed number of applications, would be helpful and impressive.

Choice of Preservative

Addition of a bacteriostatic preservative to compounded ophthalmic solutions would not satisfy the FDA requirement that ophthalmic solutions should be sterile. Addition of some preservatives in concentrations that would be bactericidal as well as bacteriostatic might introduce other factors that might be chemically or therapeutically disturbing. Furthermore, before the pharmacist can institute even such a change in the established prescription-compounding practice, he must consider several factors.

1. If the prescribed medicinal can prevent the growth of microorganisms at the requested concentration, no other preservative is needed.

2. Should the pharmacist wait until the prescribing physician has been educated to include a preservative in the requested ophthalmic preparations? The pharmacist might suggest such an addition; or he might discuss with the physician the value of using a stock solution of the preservative as the vehicle for ophthalmic solutions.

3. The preservative should not interfere with the therapeutic activity or the chemical stability of the medicinal agent. As a general rule, the therapeutic activity of ophthalmic medicinals is not disturbed appreciably by the commonly used chemical preservatives unless a chemical incompatibility exists.

4. The preservative should be used in a concentration that will be harmless to the patient but will be strong enough to exert its bacteriostatic, fungistatic, or its bactericidal effect.

The A.PH.A. Laboratory has tested a number of recommended preservatives in solutions of many medicinal agents in order to obtain information about their chemical compatibility. The preservatives and their concentrations in the solutions observed are:

Benzalkonium Chloride	1:5000
Chlorobutanol	0.5 %
Methylparaben	0.18%
andr Propylparaben	0.02%
Phenol	0.5 %
Phenylethyl Alcohol	0.5 %
Thimerosal	1:20,000

TABLE I.—MEDICINAL AGENTS ADDED TO SOLUTIONS OF PRESERVATIVES

	Concn., %		Concn., %
Antipyrine	1.0	Procaine Hydrochloride	1.0
Atropine Sulfate	1.0	Quinine Urea Hydrochloride (in Ringer's Solution No. 1)	1.0
Benzyl Alcohol	1.0	Silver Nitrate	1.0
Boric Acid	4.0	Silver Protein, Mild	10.0
Butacaine Sulfate	1.0	Sodium Benzoate	1.0
Caffeine	1.0	Sodium Bicarbonate	1.0
Chlorobutanol	0.5	Sodium Biphosphate	1.0
Dextrose	5.6	Sodium Borate	1.0
Emetine Hydrochloride	1.0	Sodium Chloride	0.9
Ephedrine Hydrochloride	3.0	Sodium Citrate	1.0
Ephedrine Sulfate	3.0	Sodium Nitrate	1.5
Fluorescein Sodium	2.0	Sodium Phosphate	1.0
Formin	1.0	Sodium Sulfadiazine	5.0
Homatropine Hydrobromide	2.0	Sodium Sulfathiazole	5.0
Hyoscine Hydrobromide	0.5	Sodium Sulfite	1.0
D-Lactose	1.0	Sodium Thiosulfate	1.0
Mercuric Chloride	1.0	Sucrose	1.0
Mercuric Succinimide	1.0	Tetracaine Hydrochloride	1.0
Metycaine Hydrochloride	2.0	Urea	1.0
Nupercaine Hydrochloride	1.0	Zinc Sulfate	1.0
Phenacaine Hydrochloride	1.0	Zinc Sulfate	1.3
Phenobarbital Sodium	1.0	and Boric Acid	2.0
Physostigmine Salicylate (with Sodium Bisulfite 1.0)	0.5	Zinc Sulfate,	0.144
Pilocarpine Hydrochloride	1.0	Boric Acid,	2.16
Potassium Iodide	1.4	and Sodium Chloride	0.216

The substances that were added to the stock solutions of the different preservatives, in order to prepare 50 cc. of each test solution, are listed in Table I. The substances listed in the "medicinal agents" include some that are used therapeutically, or as stabilizers and buffers, and some compounds that were added to broaden the compatibility study. The latter is true in those

(*Continued on page 524*)

CLINICAL CENTER, NATIONAL INSTITUTES OF HEALTH *Dedicated*

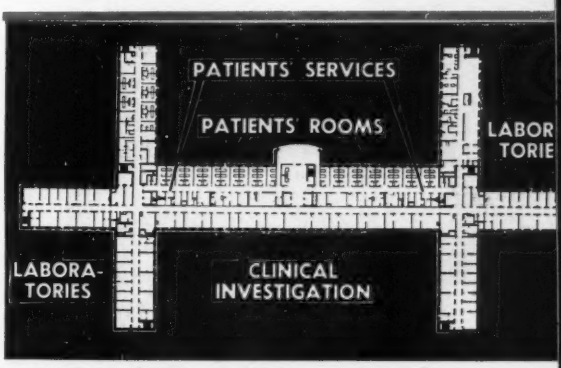
Important new medical center, housing hospital, clinic and research laboratories expected to contribute much to our knowledge of major diseases.

On July 2, 1953, the Clinical Center of the National Institutes of Health, Public Health Service, U.S. Department of Health, Education, and Welfare, was dedicated in Bethesda, Md. Mrs. Oveta Culp Hobby, Secretary of the Department of Health, Education, and Welfare, delivered the main address, and Dr. W. H. Sebrell, Jr., Director of the National Institutes of Health, and Dr. Leonard A. Scheele, Surgeon General of the U.S. Public Health Service, spoke briefly during the ceremonies.

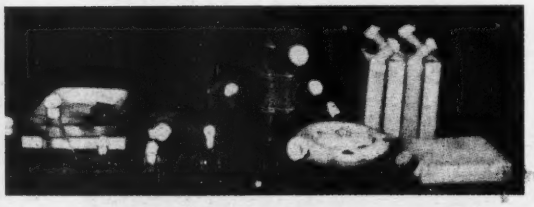
In her remarks, Mrs. Hobby pointed out the purpose of the Center will be to facilitate and improve medical research, and the Center itself is merely a part of a research program begun since the close of World War II. "We are now carrying on in the United States," Mrs. Hobby told the thousands who attended the dedicatory ceremonies, "the most intensive and widespread research attack on human disease which the world has ever seen. It is a collaborative effort—a close partnership between the Federal Government and the medical, research, and related professions, universities, and medical schools, and numerous nation-wide organizations of citizens."

The Department of Health, Education, and Welfare now supports seven research institutes, all of them located in Bethesda, a suburb of Washington, D.C. The Clinical Center is the latest of these institutes to be completed. Money for the building was first appropriated in 1947, and in its completed form, it is actually a set of laboratories surrounding a 500-bed hospital. The plan of a typical floor in the 14-story research hospital is shown below.

The special function of the Clinical Center was clearly defined at the dedicatory services by Mrs. Hobby, when she said, "This will be far more than simply another Federal Hospital. All its patients will be referred by special medical sources and chosen on the basis of the relation of their disease to problems currently under study at the Center. Teaching hospitals and specialists in the various chronic diseases will not only refer their patients here for study, but through consultation and observation will actively take part in the studies being carried on."



Although patient areas are isolated from any disturbance by laboratory traffic, the nearness of patient services and laboratories is illustrated by the typical floor plan. Clinicians can readily confer with other investigators in the 14-story Clinical Center.



Some of the penicillin culture vessels first used by Oxford research group, England. Rectangular ceramic vessels, right, were specially made when bedpans, first used, were in short supply in England.

antibiotic exhibit

AT SMITHSONIAN

Special display traces the 25 year history of antibiotics since Dr. Alexander Fleming first discovered penicillin in 1928.

One display, shown above, contains Fleming's original mold, circle, center left, and Waxman's notebook and shaking machine, lower right. Dosage samples of all antibiotics are on shelf at right, beneath chart of discovery dates.

THE U. S. National Museum, Smithsonian Institution, has opened its first exhibit of antibiotics, in observance of the 25th anniversary this year of the discovery of the "wonder drug" penicillin. The exhibit was assembled by George Griffenhagen, associate curator of the Museum's Division of Medicine and Public Health, and is located in the Smithsonian's Arts and Industries Building, which alone draws more than $1^1/_2$ million visitors a year.

The new exhibit traces the history of antibiotics and includes several unique specimens of these drugs and pertinent equipment. It was in 1928 that Prof. Alexander Fleming, of the St. Mary's Hospital in London, accidentally allowed several of his petri dishes on which disease-producing organisms were growing to remain uncovered before an open window, and the next day it was found that they had been contamined with an air-borne mold from which penicillin was eventually isolated. Instead of throwing these dishes away, he observed that wherever the mold had begun to grow the bacteria colonies either shrank or disappeared. Recognizing the importance of this observation, he named the chemical substance which the mold produced, penicillin, and announced his discovery to the world the following year. On the 25th anniversary of this discovery, Sir Alexander Fleming has donated to the Smithsonian Institution a specimen of this original mold for the antibiotic exhibition.

Antibiotics were proposed as early as 1877, when Pasteur observed that common bacteria have the property of killing anthrax germs. Twelve years after Pasteur had first discovered the phenomenon, Vuillemin, another Frenchman, coined the word "antibiosis" from the Latin word "anti" meaning against and the Greek word "bios" meaning life.

Fleming
Penicillin
1929

Florey
Penicillin Ext.
1940

Waxman
Streptomycin
1944

Burkholder
Chloromycetin
1947

Duggar
Aureomycin
1948

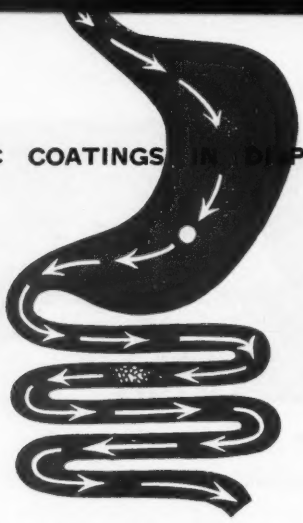
Photographs courtesy Smithsonian Institution

According to Griffenhagen, it was not until 1941, however, that Dr. Selman A. Waksman, of Rutgers University, coined the term "antibiotics" for these "wonder drugs." Dr. Waksman also comes in line for an anniversary this year, for it was ten years ago that he discovered the second important antibiotic, streptomycin. Dr. Waksman has also donated to the Smithsonian several original pieces of laboratory equipment, including the original shaking machine for the first manufacture of a submerged culture. Before this time molds were grown in flat vessels, such as those given to the Smithsonian by Sir Howard Florey, of Oxford, England, in which the first large-scale manufacture of penicillin was made, starting on Christmas Day, 1940. Mold requires oxygen to live, and until oxygen was circulated throughout the liquid media, mold would grow only on the surface of the liquid.

The evolution of the many other antibiotics, such as chloramphenicol discovered by Dr. Paul R. Burkholder in 1947, aureomycin discovered by Dr. Benjamin M. Duggar in 1948, and terramycin discovered by Dr. A. C. Finlay and his group in 1950, are all traced in the Smithsonian exhibition.

Like most great scientific and medical discoveries, the antibiotics have received much discredit, largely through misuse and misunderstanding. On this anniversary, Griffenhagen believes they should be re-evaluated as one of the greatest single advancements ever made in medical science. There is scarcely a person who does not know of someone whose life has been saved or extended by these "wonder drugs." As for the future, scientists believe that inasmuch as there are still thousands of micro-organisms yet to be classified and tested, there will doubtless be many more antibiotics discovered in the years to come, and perhaps one or more of these will replace all their predecessors.

Second exhibit contains original aureomycin soil samples; the original porcelain culture pan, with photo showing similar pans in use. F.D.A. test samples are at center right, and chloromycetin extraction process center, left.



ENTERIC COATINGS IN DISPENSING PHARMACY 1

THE PRELIMINARY INVESTIGATION

BY CHARLES W. BAUER† and ROBERT J. GERAUGHTY‡

THE search for a good enteric coating that can be used by the retail pharmacist has been in process for many years. In 1890 Ceppi introduced salol for this purpose (1). Salol is still being used as an enteric coating by the pharmacist, not because it is a good enteric coating, but because it is the only one available to him. The better known formulas of good enteric coatings reported in the literature require special equipment and can be used only where large-scale production is feasible.

It is generally agreed that a good enteric coating should have the following properties:

1. It must be non-toxic.
2. It must be physiologically inactive.
3. It must not disintegrate in the stomach.
4. It must disintegrate in the intestine.

In the final stages of this investigation special attention was given to a fifth property.

5. It must be suitable to the retail pharmacist.

A formula for an enteric coating that meets all of these specifications has been developed.

Many of the formulas for enteric coatings now being used meet some of these specifications, but none meets all five of them.

A true evaluation of an enteric coating cannot be made on *in vitro* studies alone for many of these studies used in the evaluation of enteric coatings are based upon the erroneous assumption that the contents of the intestine are alkaline in behavior (2, 3). The formula for the enteric coating reported in this investigation was submitted to *in vivo* as well as to *in vitro* studies.

It is pointed out also that an enteric coating cannot be evaluated by an investigation of the individual component parts, but by the formula in its finished form. For example, waxes resist digestion in the intestine as well as in the stomach; yet if the wax is mixed in the right proportion with certain esters, the intestinal lipase action on the esters causes a break in the coating and disintegration takes place.

A number of substances that resist change in the gastro-intestinal tract but which are absorbed into the blood stream and eliminated in the urine without undergoing further change were investigated. It was felt that these substances might be useful components of a good enteric coating. No satisfactory formula using these substances was found; but the work is reported in hope that it may help other workers in this field of investigation.

Experimental

A number of "detoxication products" were tried as enteric coatings with no success. However, hippuric acid did give encouraging results which may eventually be found to be of value in these formulas. Schoenheimer, Rittenberg, Fox, Keston, and Ratner, in 1937, reported that by using both isotopic hydrogen and nitrogen as markers about 75 per cent of the hippuric acid administered to rats was excreted in the urine without undergoing hydrolysis (4). Furthermore Quick (5) found that 2 Gm. of sodium benzoate ingested by human beings was almost quantitatively excreted as hippuric acid in the urine. It is doubtful if the amount of hippuric acid (or of benzoic acid, if it is formed) would be toxic or would have a significant physiological effect in the quantities that would be ingested by taking tablets coated with this substance.

A series of enteric coating formulas in which hippuric acid was used with different solvents and

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Presented before the Section on Practical Pharmacy, A.PH.A. Convention, Philadelphia, Pa., August, 1952.

† Former graduate student, Massachusetts College of Pharmacy, Boston, Mass.

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in various combinations with other substances were investigated. The solvents used were ethyl alcohol, methyl alcohol, isopropyl alcohol, absolute alcohol, ether, ethyl acetate, a mixture of methyl alcohol and ethyl acetate, and a mixture of ethyl alcohol and ethyl acetate. Various combinations of hippuric acid with stearic acid, cetyl alcohol, and rosin were also made. The running powders used were talc, calcium stearate, and magnesium stearate. The only formula that showed any promise consisted of a saturated solution of hippuric acid and cetyl alcohol in ethyl alcohol.

The maximum weight of this enteric coating that could be applied to a 5-gr. sodium salicylate tablet was 0.6 gr. It was further found that five coatings gave the maximum increase in weight. When these tablets were submitted to *in vivo* tests, the disintegration time was irregular and ranged from one to four hours. It was also found that the coating did not stand up on aging but became brittle and no longer offered protection against disintegration in the stomach.

A number of other substances behave as hippuric acid does in that they are eliminated in the urine in the same form in which they are ingested. Among these substances are anthranilic acid, nicotinuric acid, phenaceturic acid, cinnamyluric acid, *p*-hydroxyphenylacetic acid, and *m*-acetylaminobenzoic acid. The only other substance in this group that was tried, and that was found to be unsatisfactory by the same solvents used for hippuric acid, was anthranilic acid.

The work on "detoxication products" was very time consuming. A tablet-coating machine, a dryer, and other special equipment were necessary. The coating process was very slow, and the tablets had to be dried between coatings. At least five coats were necessary to produce tablets that were at all satisfactory.

The results obtained with hippuric acid suggest further investigation along these lines, and the work is being continued. Although in this investigation emphasis was placed on hippuric acid, other "detoxication products" may prove to be more suitable. The results of these studies will be reported in a subsequent paper if a suitable formula is developed.

At this stage of the investigation a call was made for an enteric coating that had a delayed disintegration time and that could be applied by the pharmacist. Further work on the use of "detoxication products" as enteric coatings was interrupted at this point in order to meet this challenge. Bauer and Masucci, in 1948, found that *n*-butyl stearate, applied by their method, gave a relatively heavy coating that did not disintegrate in the intestine before it reached the ileum and that in about 30 per cent of the cases it reached the colon without disintegration (2). It was felt that *n*-butyl stearate might be used in the development of a satisfactory enteric coating. The work of Bauer and Masucci (2) was repeated and their findings were confirmed.

The use of esters in enteric coating formulas is not new. It has been well established that esters with typical fat-like structures are resistant to the action of gastric contents and are readily hydrolyzed in the intestine. Esters that have a typical wax-like structure are resistant to the action of the gastric contents as well as to the action of the intestinal contents.

n-Butyl stearate[a] is neither a typical fat nor a typical wax. However, it was found to behave as a typical fat. It is resistant to the action of gastric contents and is readily hydrolyzed by the intestinal contents into *n*-butyl alcohol and stearic acid.

The non-toxic properties of stearic acid have been well established and it appears that *n*-butyl

(Continued on next page)

Authors' Summary

Most enteric coatings now in use require special equipment and are not suitable to the dispensing pharmacist.

Heretofore salol has been the only substance suitable to the pharmacist.

A new enteric coating formula has been made that has the following advantages over salol:

1. **It appears to be physiologically inactive.**
2. **It is not so time consuming.**
3. **It is suitable to the pharmacist.**
4. **It can be readily evaluated by *in vivo* tests.**

[a] *n*-Butyl stearate (Pract.) used in this investigation was obtained from The Matheson Company, Inc., East Rutherford, N.J.

• • • • • • • • • *from preceding page*

alcohol is also non-toxic in the quantities formed from the *n*-butyl stearate used in enteric coating. Weese (1928) found that *n*-butyl alcohol is completely oxidized in mice (10). Berggren (1938) found that *n*-butyl alcohol is more rapidly oxidized *in vivo* than is ethyl alcohol (11). Jenkins and Hartung (1949) in their summary of the relative toxicities of the normal primary alcohols of low molecular weight indicate that *n*-butyl alcohol is about three times more toxic than ethyl alcohol. The figure they give for the M.L.D. Gm./Kg. dog, for *n*-butyl alcohol, is 2.4. The maximum amount of *n*-butyl alcohol formed from the *n*-butyl stearate used on one enteric-coated tablet or capsule is 20 mg.

No untoward effects were noted from the use of *n*-butyl stearate-carnauba wax enteric-coated capsules or tablets in any of the more than 100 subjects used in these tests.

TABLE I.—TIME REQUIRED FOR SODIUM SALICYLATE TO APPEAR IN THE URINE WHEN ONE *n*-BUTYL STEARATE-CARNAUBA WAX ENTERIC-COATED 5-GR. SODIUM SALICYLATE *Tablet* WAS INGESTED

No. of Subjects	No. of Coatings Applied	No. Hours Required for a Positive Test							
		1	2	3	4	5	6	7	8
4	1	+	..	..	..	..	..	..	..
1	2	+	..	..	..	..	..	..	..
3	2	−	+	..	..	..	..	..	..
4	3	−	−	−+	..	..	..	..	..
19	3	−	−	−	+	..	..	..	..
5	3	−	−	−	−	+	..	..	..
1	3	−	−	−	−	−+	..	..	..
1	4	−	−+	..	..	..	..	..	..
1	4	−	−	−	+	..	..	..	..
2	4	−	−	−	−	+	..	..	..
10	4	−	−	−	−	−	+	..	..
3	4	−	−	−	−	−	−	+	..
2	4	−	−	−	−	−	−	−	−

TABLE II.—TIME REQUIRED FOR SODIUM SALICYLATE TO APPEAR IN THE URINE WHEN ONE *n*-BUTYL STEARATE-CARNAUBA WAX ENTERIC-COATED 5-GR. SODIUM SALICYLATE *Capsule* WAS INGESTED

No. of Subjects	No. of Coatings Applied	No. Hours Required for a Positive Test							
		1	2	3	4	5	6	7	8
2	3	−	+	..	..	..	..	..	..
2	3	−	−	+	..	..	..	..	..
12	3	−	−	−	+	..	..	..	..
4	3	−	−	−	−	+	..	..	..
1	4	+	..	..	..	..	..	..	..
2	4	−	+	..	..	..	..	..	..
2	4	−	−	+	..	..	..	..	..
6	4	−	−	−	−	+	..	..	..
3	4	−	−	−	−	−	−+	..	..
5	4	−	−	−	−	−	−	−	−

TABLE III.—THE EFFECT OF DIFFERENT SOLVENTS ON THE *n*-BUTYL STEARATE-CARNAUBA WAX ENTERIC-COATED SODIUM SALICYLATE TABLETS

Solvent	Disintegration Time in Hours							
	1	2	3	4	5	6	7	8
Distilled water	−	−	−	−	−	−	−	−
Hydrochloric acid pH 3	−	−	−	−	−	−	−	−
Sodium bicarbonate solution pH 8	−	−	−	−	−	−	−	−
Artificial gastric juice	−	−	−	−	−	−	−	−
Old type artificial intestinal juice pH 8	+	..	..	..	..	..	..	..
New type artificial intestinal juice pH 6.8	+	..	..	..	..	..	..	..

It was felt that a mixture of *n*-butyl stearate with carnauba wax would give a mixture that would lend itself to the "dip method" of applying the coatings. Various combinations were tried, and the most satisfactory formula found is the following:

n-Butyl Stearate.....70 parts
Carnauba Wax.....30 parts

This mixture melts at 74°. By holding the temperature at 78° one can easily dip the capsule or tablet into this mixture. On withdrawing the capsule or tablet, the mixture readily solidifies in a few seconds. The second, third, and fourth coatings can be readily applied. A number 2 capsule increases in weight about 50 mg. for each dipping.

In vivo tests with coated sodium salicylate tablets and capsules were carried out. Sodium salicylate was easily detected in the urine by the method of Lazenski and Diver (6). The bladder was emptied previous to the test. Samples of urine were then tested at half-hour intervals. Ten-cc. samples were used. The samples were acidified with dilute hydrochloric acid, and ten drops of a 10 per cent ferric chloride solution were added. A positive test was evidenced by a purple color which developed immediately if disintegration had occurred.

It was found that the average disintegration time of three coatings in *in vivo* tests is about four hours and that the disintegration time of four coatings is about six hours. The results of these tests are shown in Tables I and II.

The butyl stearate-carnauba wax enteric-coated capsules and tablets were also submitted to *in vitro* tests at 37° in the following solvents.

Distilled water
Diluted hydrochloric acid, pH 3
Diluted sodium bicarbonate, pH 8
Artificial gastric juice (7, 2)
Old type artificial intestinal juice (8, 2)
New type artificial intestinal juice (9, 2)

The results of these tests are shown in Table III.

These results shown in Tables I, II, and III indicated that this enteric coating withstands disintegration in the stomach but does disintegrate in the intestine. The results further indicate that the disintegration is due to the action of the intestinal enzymes. It is further indicated that carnauba wax does not interfere with the disintegrating action of the intestinal enzymes upon the *n*-butyl stearate.

X-Ray Visualization Studies of the *n*-Butyl Stearate-Carnauba Wax Enteric-Coating Formula

Bismuth subcarbonate tablets, 5 gr., were dipped three times, as previously explained, with the *n*-butyl stearate-carnauba wax mixture. The tablets were stored at room temperature for three weeks. After this period the coating showed no signs of cracking. Four normal adult subjects were given two tablets each. The place and time of disintegration were determined by X-ray visualization studies by Dr. Harry Shwachman and Dr. Charles W. Weill of the Children's Hospital in Boston. In no case did the tablets disintegrate in the stomach. The longest period of time any tablet remained in the stomach was three hours. In all cases the tablets disintegrated in the jejunum between three and four hours after ingestion.

These studies confirm the earlier findings of the *in vivo* studies of this coating when it was applied to sodium salicylate capsules and tablets.

Stability of the *n*-Butyl Stearate-Carnauba Wax Enteric Coating

It was found that cracks appeared in the coating after a period of four weeks when stored at room temperature. This indicates a limited use of this enteric coating. It is felt that the use of a plasticizer will overcome this handicap. It is also felt that by altering the proportions of the *n*-butyl stearate, carnauba wax, and a plasticizer the time of disintegration may be delayed.

Discussion

In the search for a good enteric coating which could be used by the pharmacist it was necessary to consider the coating from the point of view of the dispensing pharmacist. No elaborate equipment should be required, the application of the coating should not be too time-consuming, and the coating should be easy to apply. The *n*-butyl stearate-carnauba wax mixture meets all these requirements.

The following prescriptions were taken from the files of a drug store, over a six months' period, to illustrate the demands for enteric coatings.

1. Ferrous Sulfate 5.00
   Arsenious Acid 0.06
   Strychnine Sulfate 0.075
   Make 50 enteric-coated pills.
   Signa: One before meals.

(*Continued on page 512*)

ENTERIC COATINGS IN DISPENSING PHARMACY — 2

A PRACTICAL METHOD OF EXTEMPORANEOUS ENTERIC COATING

BY MITCHELL J. STOKLOSA and† LESLIE M. OHMART‡

THE preliminary investigation of the *n*-butyl stearate-carnauba wax enteric coating has suggested the adaptability of the mixture to the extemporaneous coating of capsules, a purpose for which the dispensing pharmacist usually employs salol, since it is one of the very few enteric agents that he can apply successfully to dosage forms. In that study a formula consisting of 70 parts of *n*-butyl stearate and 30 parts of carnauba wax was evaluated for certain essential properties, both physical and physiological, and it was found that the coating would lend itself to easy application by dipping dosage forms in the melted mixture. The method of application, which is mentioned only briefly in the preliminary paper, will be described in detail in this report since its

(*Continued on page 514*)

Presented before the Section on Practical Pharmacy A.PH.A. Convention, Philadelphia, Pa., August, 1952.
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‡ Chairman, Department of Pharmacy, Massachusetts College of Pharmacy, Boston, Mass.

FROM THE SECRETARY'S DIARY FOR JULY, 1953

2nd Today at the National Institutes of Health in Bethesda where the new experimental Clinical Center was dedicated. Among the other features of this highly modern hospital installation is a most up-to-date pharmacy, under the very competent supervision of Milton Skolaut.

6th The mail and the telephone unusually heavy, as might be expected after the holiday and with the Convention coming along as fast as it is. Also the battle behind the scenes in connection with the Factory Inspection Amendment to the Food, Drug, and Cosmetic Act keeps pace with July's mounting temperature and humidity.

11th Now completing a week of conferences with a meeting of the Policy Committee of our Division of Hospital Pharmacy. In addition to members of the committee, Dr. Charles Letourneau of the American Hospital Association was a visitor, and a busy day was spent reviewing such hospital pharmacy problems as internship standards, narcotic regulations, hospital pharmacy institutes, census data, hospital formularies, and graduate courses in hospital pharmacy. In the evening a pleasant visit with Dean Jenkins of Purdue.

12th Much of this day spent at Walter Reed Hospital and learning much from Capt. John McNamara, who has developed a splendid hospital service at this army medical center and who will be sorely missed when he leaves in the near future for a new assignment.

13th All this day struggling with the meeting room assignments and program details for the Salt Lake City Convention. Much of this is difficult under any circumstances, but it becomes more so when the place of meeting is at such a great distance from headquarters. However, local cooperation is on a high level and that is always a great help.

14th Now some last minute calls for papers to go on programs of the various Sections; also corrections on the programs already in type. But this is nothing unusual and the Section Secretaries are cooperating beautifully to complete the Abstracts so that our service should be satisfactory to all concerned.

16th Now working on the laminated Code of Ethics Souvenir to be distributed at the coming Convention, and in the afternoon to the House of Representatives to listen to the debate on the "factory inspection amendment." As one after another of the members of the Committee on Interstate and Foreign Commerce and other congressmen arose to express their views on what the amendment means, it becomes quite clear that the congressional intent will be properly stated for the benefit of the courts. Practically every man who spoke let it be known that "factories" referred to in this bill does not mean retail pharmacies.

17th Today completing the mailing of Abstracts and proposed By-Laws to the members of the Scientific Section and looking forward to the time when all Sections will have their abstracts ready for publication in time for distribution to members of record in advance of the Convention. Perhaps we can also hope for the day when all committee reports will be ready in advance for mailing to members of the House of Delegates for study before action at the Annual Meeting.

18th A Saturday at the office with conferences on collection and arrangement of ASSOCIATION archives, with George Griffenhagen and Alex Berman. Also conferring on hospital pharmacy problems with officers of the American Society of Hospital Pharmacists and glad of the opportunity to finish Convention program details free from the telephone and other distractions.

20th In the afternoon to Philadelphia by train and then with Lou Longaker to Atlantic City in his car, and to dinner with Bert Mull, Bob Swain, Tommy Atkins, and Paul Olsen, the inimitable team which has entertained and instructed so many state pharmaceutical associations at their annual conventions. A night session with Bert Mull on details of National Pharmacy Week and other public relations problems. Bert has certainly kept his committee on the job this year, and things are moving well on schedule for an unusually good observance of this important event in 1953.

21st This morning attending the business session of the Pennsylvania Pharmaceutical Association at the Ambassador Hotel in Atlantic City and later having dinner with the past-presidents. Glad to see Charles R. Rhodes still active and interested in the proceedings of the ASSOCIATION over which he presided lo these many years ago.

22nd Now working with the lawyers on the By-Laws of the AMERICAN PHARMACEUTICAL ASSOCIATION Foundation and also conferring with representatives of the National Research Council and the U.S. Public Health Service on international pharmaceutical problems, generic names for drugs and related matters.

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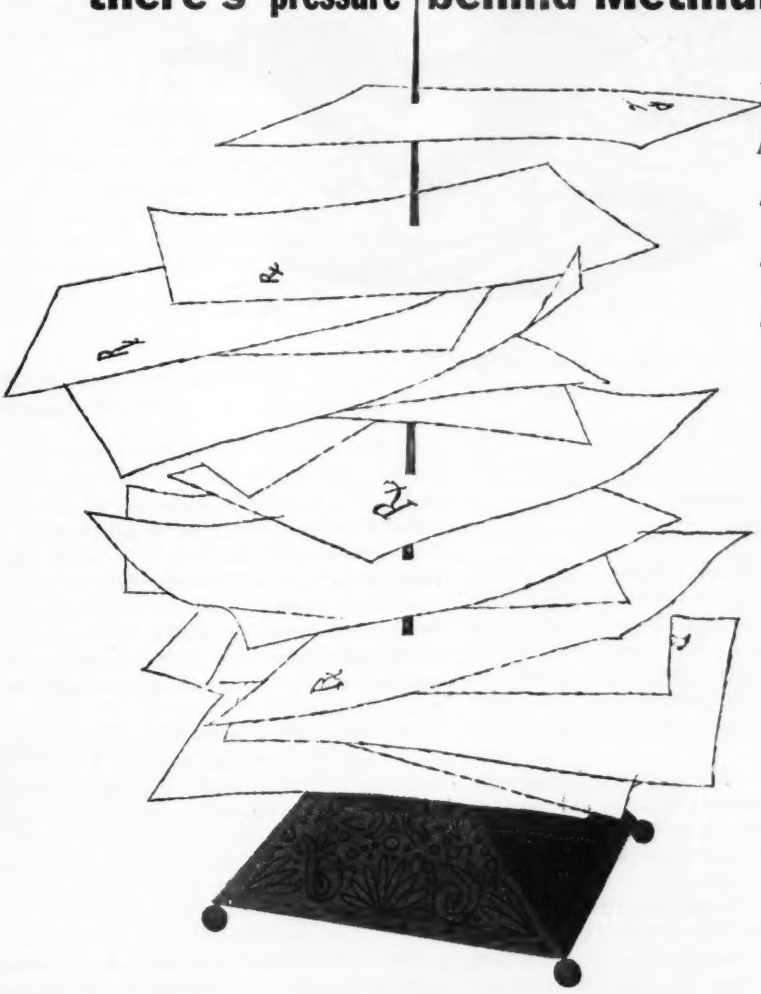

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FCDA Describes Atomic Radiation Problems

Federal Civil Defense Administration recently noted the sharp differences between peacetime radiation safety levels and those under which Civil Defense forces would operate in an atomic attack. The comment came July 6, with the release of a technical bulletin to the Nation's CD officials on "Emergency Exposures to Nuclear Radiation."

The scientific test data on radiation, as it would have affected human beings in the test houses of Operation Doorstep, March 17, at the Nevada Proving Grounds, was again called to the attention of the CD officials.

The portion of the test concerned with radiation produced these conclusions:

"1. While the contamination of the FCDA area was inconvenient for both observers and program personnel, *it would not have seriously hampered Civil Defense disaster operations in a real emergency.*

"2. Persons in the first- and second-floor rooms of the near house would have received a severe dose of initial radiation from the burst. This dose would have been sufficient to cause serious radiation sickness *with the probability of death in some cases.* Persons in the basement shelters of the near house would have been almost completely protected from the initial radiation. However, had persons taking shelter in the basement been forced to remain for the 30-hour period before the badges were recovered, an unlikely contingency, some cases of radiation sickness from exposure to residual radiation might have resulted with recovery expected in most cases.

"3. Persons in the first- and second-floor rooms of the house at 7,500 feet *would not have received enough initial radiation to be of consequence.* Persons in the basement should have received no initial dosage, and even 30 hours' exposure to residual activity should not have seriously endangered them.

"4. Persons in any of the outdoor shelters would have received *good protection from initial radiation,* but *some* probably would have become casualties from residual radiation over a 30-hour period."

FCDA Releases Film on Atomic Test

The Federal Civil Defense Administration announced today the release of a motion picture of the March 17 test at Yucca Flat, Nev., where two frame houses, various home shelters, and automobiles were exposed to an atomic blast. The film was produced without cost to the Government by Byron, Inc., with the cooperation of FCDA. Prints are being distributed to regional and state civil defense directors, and to television stations throughout the United States and its Territories.

The film supplements the booklet, "Operation Doorstep," a preliminary report on the test, issued by FCDA. Copies of the film may be bought from Byron, Inc., 1226 Wisconsin Ave., N.W., Washington, D.C., for $27 each. The price includes reel, can, and shipping case.

Military Blood Centers Discontinue Collections

In the light of diminishing blood needs for the Armed Forces and the demonstrated ability of the Red Cross to meet these requirements, the Department of Defense recently announced temporary discontinuance of collections at blood donor centers on Armed Forces installations throughout the United States.

The announcement emphasized that there is a continuing need for whole blood and that the American National Red Cross will continue to collect whole blood to fill the Armed Forces requests.

FCDA Head Says CD Proved Worth in Disasters

Governor Val Peterson, FCDA Administrator, noting the approaching end of the "tornado season" recently said, "These terrible catastrophes have clearly shown that the same men and women who are organized, equipped, and trained to counteract an atomic blast are effective on the home front in times of flood, earthquakes, and tornadoes. Civil defense volunteers and officials in the disaster areas are deserving of the highest praise."

Under the Disaster Act—Public Law 875 as amended—the President has delegated certain authority to the FCDA to act for him in natural disasters, whenever the governor of any state requests Federal assistance. The governor's request is turned over to the FCDA for study and recommendations on action and granting of funds.

The Administrator becomes responsible for the expenditure of disaster funds authorized by the President. His statutory responsibility is to provide "maximum mobilization of Federal assistance" in equipment, supplies, facilities, personnel, and other resources; to undertake work essential to the preservation of life and property, the clearing of debris, the emergency repair or temporary replacement of public facilities. He may distribute medicine, food, or other supplies.

Because of its regional organization, FCDA has been able to assemble recommendations for action from its specialists at the scene, and to evaluate them rapidly for the President, while disasters struck, one after another or even at the same time, at different points.

Floods which have had FCDA attention occurred during the past five months in Louisiana, Montana, Texas, Kansas, North Dakota, Georgia, Oklahoma, Maine, Iowa, Wisconsin, New Hampshire, Nebraska, Mississippi, and California.

Tornadoes struck in Georgia, Nebraska, Minnesota, Texas, Michigan, Ohio, Massachusetts, Alabama, and Tennessee.

Governor Peterson said he does not regard the $10,000,000 administered in "preliminary allocations" as the agency's principal contribution. "The various and widespread Federal services which we have been able to mobilize and coordinate immediately at the disaster scene are even more significant," he said.

Clemmense M. White Appointed New Head of FCDA Educational Services

The appointment of Clemmense M. White of St. Joseph, Mo., to be an Assistant Administrator, was announced recently by Federal Civil Defense Administrator, Val Peterson. Colonel White heads the Civil Defense Educational Services, comprising Public Affairs, Training and Education, and Publications. He succeeds Mrs. Katherine G. Howard of Boston, who has become Deputy Administrator to Governor Peterson.

Dentists Told How to Help Civil Defense

How dentists can help in the civil defense casualty services program and what training they should have to perform their duties are described by the Federal Civil Defense Administration in a new technical manual, "The Dentist in Civil Defense."

The manual points out "in a major disaster the number of available physicians and nurses would be far too few to provide even emergency relief" and that dentists could give valuable auxiliary medical service if they had previous casualty-care training.

The American Dental Association has approved the recommendations in the manual. It was written by Russell W. Bunting, former Dean of the School of Dentistry, University of Michigan, an FCDA consultant, and is being distributed to regional, state, and local civil defense offices, and to dental associations. Copies are on sale for 15 cents each by the Superintendent of Documents, Washington 25, D.C.

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Enteric Coating I

• • • • • • • • • • • • • *from page 507*

2. Digitalis Pills.....0.100
   Make 50 enteric-coated pills.
   Signa: One t.i.d.

3. Caffeine.....0.03
   Powdered Digitalis 0.09
   Make 20 such enteric-coated pills.
   Signa: One t.i.d. p.c.

4. Powdered Opium.....2.00
   Make 20 enteric-coated capsules.
   Signa: One every four hours.

5. Ammonium Chloride.....0.600
   Make 36 enteric-coated capsules.
   Signa: One t.i.d.

6. Methenamine.....0.300
   Make 12 enteric-coated capsules.
   Signa: One every four hours.

In each prescription the pharmacist used a salol coating because no other coating was available, and because none of these medications was obtainable from drug manufacturing houses in the dosage form indicated.

It is believed that the *n*-butyl stearate- carnauba wax mixture not only offers distinct advantages over salol for enteric coating in the retail drug store, but that it may suggest other coatings to the pharmacist which he may wish to evaluate.

X-ray visulization studies are good but are time consuming, expensive, require a certain amount of skill, and must be done under the supervision of an experienced operator. *In vivo* tests on enteric-coated sodium salicylate tablets by the method indicated have given practically the same values as were obtained by fluoroscopic visualization tests of the same enteric coating. This method is recommended to the pharmacist who wishes to make preliminary investigations in this field.

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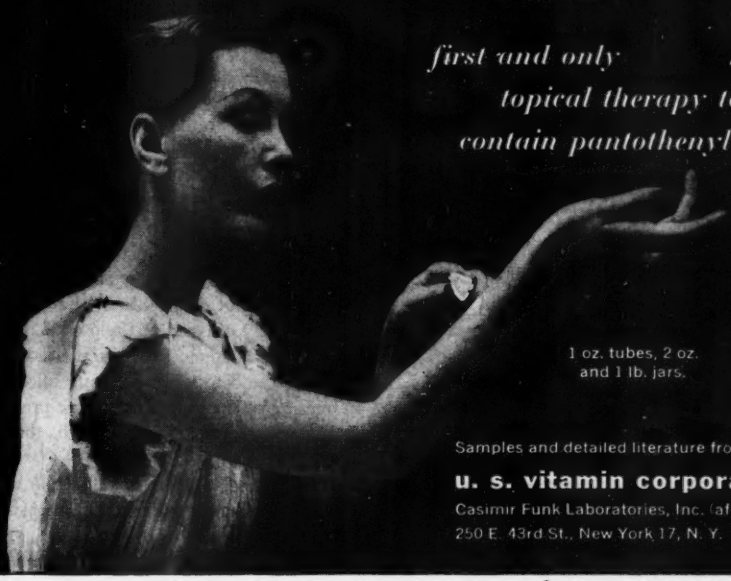

1 oz. tubes, 2 oz.
and 1 lb. jars.

Samples and detailed literature from
u. s. vitamin corporation
Casimir Funk Laboratories, Inc. (affiliate)
250 E. 43rd St., New York 17, N. Y.

TABLE I

	Coating												
	1	2	3	4	5	6	7	8	9	10	11	12	13
n-Butyl Stearate	46	45	40	30	45	45	45	45	45	45	45	45	45
Carnauba Wax	31	30	..	..	..	..	30	30	30	30	30	30	30
Paraffin	23	20	..	20	30	30	..	..	22	20	20	20	20
Yellow Wax	..	5	..	5	..	..	..	..	..	..	..	..	..
Wool Fat	..	..	..	..	..	..	..	..	3	..	..	..	..
Candelilla Wax	..	..	60	45	..	..	..	..	..	..	..	..	..
Glyceryl Monostearate	..	..	..	..	25	..	..	..	..	5	..	..	..
Diglycol Stearate	..	..	..	..	..	25	..	..	..	..	5	..	..
Cetyl Alcohol	..	..	..	..	..	..	25	..	..	..	..	5	..
Stearic Acid	..	..	..	..	..	..	..	25	..	..	..	..	5

Enteric Coating II

••••••••••••••*from page 507*

development constituted one of the purposes of this investigation.

In order to further evaluate certain physical properties of the *n*-butyl stearate-carnauba wax mixture, it was suggested that the stability of the coating under ordinary conditions of storage should be determined. Accordingly, a number of capsules were coated with the mixture and then subjected to stability tests in an attempt to determine the effect of variations in temperature on the coating. It was noted that cracks or fissures developed in the shell in about four weeks when the capsules were stored at room temperature, and in a considerably shorter time when they were subjected to a temperature of 0° C.

Recognizing the limitations of this enteric agent if variations in temperature caused the coating to fissure and thus to become discontinuous, a study was undertaken to determine if the addition of certain substances would plasticize the mixture sufficiently to eliminate the tendency of the coating shell to crack without significantly affecting its physiological properties.

Experimental

A series of coatings was prepared according to the formulas given in Table I. The quantities refer to parts by weight.

It should be noted that most of the substances used in the attempt to impart some degree of plasticity to the original coating were soft, waxy solids which in themselves are not or do not become brittle. Some of the materials chosen have been described as enteric agents or have been used as ingredients in enteric coatings.

Each coating was prepared by fusing the ingredients, straining the mixture if necessary, and allowing the mixture to congeal. The coatings were applied to sodium salicylate capsules. In each instance, three lots of capsules were coated, the first by applying two coatings; the second, three coatings; and the third, four coatings. This was done in order to determine if the thickness of the coating was a factor in the cracking of the shell.

Method of Application of the Coating to Capsules

The coating mixture, contained in an evaporating dish, was heated on a water bath to about 75° C. and maintained at that temperature during the coating process. The coating was then applied in the following manner. The capsule to be coated was grasped at one end with a pair of tweezers and dipped into the melted mixture to a depth sufficient to coat approximately one-half of it. As the capsule was withdrawn, it was touched to the lip of the dish to catch the rundown. The coating solidified almost immediately, allowing the operator to place the capsule on a glass slab and to insert the next capsule into the jaws of the tweezers. In this manner one end of all of the capsules in a lot was coated. Each capsule was then carefully grasped at the coated end with the tweezers and dipped into the melted mixture to complete the coating, care being taken to insure an overlap of the dipping over the preceding one. The cycle was repeated until two, three, or four coatings were applied.

This method of application, while very useful for the extemporaneous coating of capsules, is not, in the opinion of the investigators, satisfactory for the coating of tablets which are discoid in shape. Although tablets coated by this method

may possess the essential physiological properties, it is felt that their physical appearance would not be pharmaceutically acceptable.

The coatings were evaluated on the basis of their adaptability to this method of application, and the coated capsules were observed for fissuring when stored at room temperature and at 0° C. Mixture 8 was the most satisfactory one, and capsules with two coatings of the mixture showed no signs of cracking at the end of four weeks.

In order to evaluate the efficiency of the coating and to determine whether the addition of stearic acid affected the disintegration time of the *n*-butyl stearate-carnauba wax mixture as described in the preliminary investigation, *in vivo* tests using sodium salicylate capsules with two coatings of mixture 8 were carried out. Four subjects were used, and the time required for sodium salicylate to appear in the urine when one capsule was ingested was between four and five hours in all cases.

The coating was then subjected to fluoroscopic visualization studies. Barium sulfate capsules with two coatings of the mixture were given to nine subjects, and the place and time of disintegration were observed. The results of these observations are given in Table II.

TABLE II

Subject	Number of Capsules Taken	Place and Time of Disintegration
A	2	2 capsules in intestinal tract intact after 6 hours
B	2	2 capsules in intestinal tract, about 4 1/2 hours
C	2	1 capsule high in intestinal tract intact after 6 hours 1 capsule low in intestinal tract intact after 6 hours
D	2	2 capsules in intestinal tract, about 4 to 4 1/2 hours
E	2	1 capsule in intestinal tract, about 5 hours 1 capsule in intestinal tract intact after 6 hours but less dense
F	2	2 capsules in intestinal tract, about 3 1/2 to 4 hours
G	2	2 capsules in intestinal tract, about 3 1/2 to 4 hours
H	2	1 capsule in intestinal tract, about 3 1/2 hours Position of other capsule unknown
I	2	2 capsules in intestinal tract intact after 6 hours but less dense

It will be observed from these results that, of the 18 capsules ingested, 10 disintegrated in the intestinal tract in from 3 1/2 to 5 hours, 7 were in the intestinal tract intact at the end of 6 hours, and the position of one was unknown.

Conclusions

In the attempt to impart plasticity to the *n*-butyl stearate-carnauba wax enteric coating that was studied in the preliminary investigation, it was found that a coating consisting of 45 parts of *n*-butyl stearate, 30 parts of carnauba wax, and 25 parts of stearic acid was adaptable to the method of application described in this report and that the shell on capsules with two coatings of the mixture showed no evidence of cracking at the end of the observation time. The fluoroscopic visualization studies, however, seem to indicate that the disintegration time of the coating in the intestinal tract is somewhat more delayed than that reported for the coating containing only *n*-butyl stearate and carnauba wax. It is recommended, therefore, that an extended study of the effect of varying the proportions of the ingredients in the *n*-butyl stearate-carnauba wax-stearic acid mixture on the efficiency of the coating be undertaken, and that the efficiency of the formulations be evaluated radiographically.

Authors' Summary

An enteric coating consisting of *n*-butyl stearate, carnauba wax, and stearic acid was prepared and evaluated.

A practical method of application of the coating to capsules has been described.

The results of fluoroscopic visualization studies of the efficiency of the coating have been noted.

An extended study of the effect of varying the proportions of the ingredients of the coating mixture on its disintegration time is recommended.

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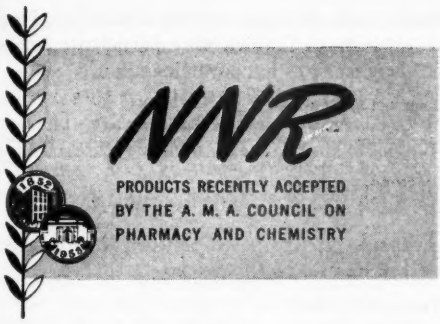

CARBACRYLAMINE RESINS.—Carbo-Resin (Lilly).—A flavored mixture of 87.5 per cent of the cation exchangers, carbacrylic resin and potassium carbacrylic resin, and 12.5 per cent of the anion exchanger, polyamine-methylene resin. Two-thirds of the cation exchange mixture is carbacrylic resin (a polyacrylic carboxylic acid resin) and the remainder is the potassium salt of the carbacrylic resin.

Actions and Uses.—Carbacrylamine resins is used as an adjunct to increase the fecal excretion of sodium in the treatment of edema caused by abnormal sodium retention by the kidney. It is useful, therefore, in the management of sodium retention accompanying chronic congestive heart failure, cirrhosis of the liver, and the nephrotic syndrome.

The cation exchange resin is of the carboxylic acid type that gives up its hydrogen ions in exchange for cations. Its affinity for various cations differs in accordance with their valence and their order in the atomic table. Therefore, in a solution containing equal milliequivalents or concentrations, it would combine with more calcium and potassium than sodium. However, because the concentration of sodium in the intestinal tract is relatively high, the major exchange capacity of the resin is utilized in the removal of that cation. It is estimated that in a man weighing 60 Kg. (132 lb.), approximately 160 Gm. of endogenous sodium enter the intestine every day along with the usual exogenous intake of 4 to 6 Gm. Some evidence indicates that the cation exchange resin acts chiefly on the exogenous sodium of the diet. Because of the capacity of the cation exchange resin to combine with other essential metallic ions, it has been found necessary to administer one-third of the resin as the potassium salt to prevent serum deficiency of that important cation. Carbacrylamine resins provides two-thirds of the cation exchange resin in the hydrogen form and one-third in the potassium form. The anion exchange resin makes up about one-eighth of the mixture and is added to reduce the tendency to acidosis produced by the cation exchange resin in patients with severe renal impairment caused by the inability of the kidney to manufacture sufficient ammonia. This tendency toward the production of acidosis is not obviated by the use of an ammonium salt in place of the hydrogen form of the carboxylic resin, since the ammonia which would be released is subsequently converted to urea in the liver. The anion exchange resin slightly increases the capacity of the cation exchange resin at the pH of the intestinal contents. Some investigators have observed that the cation exchange resin enhances the diuresis produced by mercurial diuretics. The use of the cation exchange resin is not intended to supplant the use of mercurial diuretics or dietary control of sodium intake. In edematous patients, who already exhibit a minimal urinary excretion of sodium prior to administration of the resin, there is little chance of producing a further reduction through the fecal diversion of dietary sodium.

Carbacrylamine resins must be employed with care to prevent the development of a low sodium syndrome, particularly in patients with an abnormal distribution of that electrolyte in the tissues. Precautions to guard against the development of acidosis are also essential. Periodic determination of the carbon dioxide combining power and serum chlorides should be made when negative sodium balance has been present for some time after edema has disappeared. Patients should also be observed regularly for signs of mineral deficiency in other cations, such as calcium. Since hyperpotassemia can occur when urinary excretion is severely limited, the mixture should be used only in patients with adequate kidney function. Use of the potassium salt form as provided by the mixture is contraindicated for patients with anuria. Salt "substitutes" containing potassium should be used sparingly, if at all, because an increase in potassium intake may reduce the efficiency of the cation exchange resin. The mixture should not be employed without adequate laboratory facilities to follow the serum electrolyte pattern. Whenever food consumption is temporarily interrupted or sodium intake reduced, the dosage of the mixture must be adjusted accordingly. Large doses may produce gastrointestinal dis-

(Continued on next page)

N.N.R.

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comfort, anorexia, nausea, and vomiting; but care is needed to differentiate such symptoms from those caused by sodium depletion. The possibility of fecal impaction in elderly patients should be kept in mind.

Dosage.—Carbacrylamine resins is administered orally as a flavored powder which can be dispersed in water. Each gram will remove approximately 1 mEq. (23 mg.) of sodium from the intestinal tract when the patient is on a diet containing at least 1.5 Gm. of sodium (3.7 Gm. of sodium chloride) per day. The number of metallic ions bound to the carboxylic resin decreases as the intake of salt is reduced. On a low sodium diet (0.5 Gm. or less), usually no more than 0.3 mEq. (7 mg.) of sodium is removed by each gram of the mixture. The total daily amount must be adjusted to meet the individual requirements of each patient. For patients with abnormal retention of sodium, who require restriction of sodium intake to 1.5 Gm. or less per day plus regular therapy with a mercurial diuretic, 48 Gm. of the drug usually will maintain an edema-free state when intake of sodium is increased to 3 Gm. (7.5 Gm. of sodium chloride) per day.

The usual initial dose is 16 Gm. (two level tablespoonfuls) suspended in 6 oz. (180 cc.) of tap water or fruit juice, three times daily, to be taken between meals. The mouth is rinsed free of the particles after each dose. Milk should be avoided because of its high electrolyte content. The suspension should be taken immediately after thorough stirring, but additional water or juice may be taken after each dose. No more than 24 Gm. is advisable for a single dose. When it is necessary to prescribe more than 72 Gm. per day, the number of doses rather than the size of the individual dose should be increased. The maintenance dosage is adjusted on the basis of constant "dry" body weight when either the dietary intake of sodium can be increased or the total dose of the resin mixture reduced until body weight rises. The dosage required to maintain a balance between intake and output of sodium should be reduced by simultaneous moderate restriction of dietary sodium or by administration of a mercurial diuretic. In some persons severely restricted previously, the moderate increase of salt permitted with the administration of the resin mixture has been followed by increase in appetite and nutrition. When edema fails to disappear during resin therapy, attention must be given to other factors which may participate in its etiology, such as hypoproteinemia.

Tests and Standards—

Physical Properties: Carbacrylamine resins is a light buff, free-flowing powder without appreciable odor. It is practically insoluble in dilute acids and alkalis, alcohol, ether, and water. All of the powder passes a 100 mesh screen and 75 per cent passes a 200 mesh screen.

[For more information regarding tests and standards and for dosage forms see *J. A. M. A.*, **151:** 210 (Jan. 17, 1953).]

CARBACRYLIC RESIN.—A polyacrylic carboxylic acid resin.

Tests and Standards—

Physical Properties: Carbacrylic resin is a free-flowing, buff powder, 99 per cent of which passes a 100 mesh screen and 75 per cent of which passes a 200 mesh screen.

[For more information regarding tests and standards see *J. A. M. A.*, **151:** 211 (Jan. 17, 1953).]

POTASSIUM CARBACRYLIC RESIN.—The potassium salt of a polyacrylic carboxylic acid resin.

Tests and Standards—

Physical Properties: Potassium carbacrylic resin is a free-flowing, buff powder, 99 per cent of which passes a 100 mesh screen and 75 per cent of which passes a 200 mesh screen.

[For more information regarding tests and standards see *J. A. M. A.*, **151:** 211 (Jan. 17, 1953).]

Eli Lilly & Company, Indianapolis.

Powder Carbo-Resin (Flavored): 450 Gm. bottles. A flavored mixture containing about 0.583 Gm. of carbacrylic resin, 0.292 Gm. of potassium carbacrylic resin and 0.125 Gm. of polyaminemethylene resin in each gram of powder.

HEXAMETHONIUM CHLORIDE.—Methium Chloride (Warner-Chilcott).—Hexamethylenebis(trimethylammonium chloride).—$C_{12}H_{30}Cl_2N_2$.—M. W. 273.29.—The structural formula of hexamethonium chloride may be represented as follows:

$$(CH_3)_3N^+\text{–}CH_2(CH_2)_4CH_2N^+(CH_3)_3\ 2Cl^-$$

Actions and Uses.—Hexamethonium chloride shares the actions and uses of other hexamethonium salts and other quaternary ammonium compounds, such as tetraethylammonium chloride, which act as ganglionic blocking agents. The drug inhibits, to a variable degree, nerve impulses transmitted through both the sympathetic and parasympathetic ganglia. When injected, its blocking effect on sympathetic stimuli causing vasospasm produces increased blood flow, especially in the lower extremities, and lowering of the blood pressure. When taken orally, the absorption of the drug is slower and its action too delayed for effective control of peripheral vascular diseases. Either the oral or parenteral route is useful in the management of moderate to severe hypertension; oral medication may be

more practical for control of moderate elevations in blood pressure, and injection for episodes of severe hypertension. The drug is less effective for mild hypertension. By either route, tolerance to hexamethonium chloride may develop with its use for hypertension because of readjustments in the vascular system. Untoward severe hypotension and peripheral circulatory collapse seldom occur with initial oral doses, but such reactions should be anticipated and minimized by appropriate care when instituting parenteral therapy.

The simultaneous blocking action of parasympathetic impulses produces atropine-like side-effects which cannot be entirely separated from the vasolytic and hypotensive action of the drug. Thus, there may be a loss of accommodation, cessation or decrease of gastrointestinal motility, and alteration of bladder function. These side-effects are seldom encountered during initial oral medication. When constipation occurs, it usually appears within the first few days and laxatives should be administered concomitantly. This prevents accumulation of the drug in the intestinal tract. Such accumulation may lead to increased absorption of the drug and to paralytic ileus. Nausea, when present, tends to disappear with continuance of therapy.

Hexamethonium chloride has no advantage and is subject to the same precautions of use as other hexamethonium salts, except that the added hazard of bromide or iodide intoxication is eliminated. The drug should be employed with caution in all elderly patients and those with arteriosclerosis; it should be used with even greater caution, if at all, in patients with myocardial or cerebral ischemia (encephalopathy) or renal failure (uremia). Serious kidney damage involves the danger of hexamethonium poisoning caused by delayed urinary excretion of the drug. Hospitalization is desirable during institution of therapy, but this is not mandatory if patients are under careful observation during initial phases of medication and blood pressure determinations are made frequently until the tolerated daily dosage is established for each patient. If fainting and vascular collapse occur, the patient should be placed in a recumbent position and his feet elevated. Phenylephrine hydrochloride, 2 to 4 mg. intravenously, may be used to combat profound hypotension; small doses should be used because hexamethonium increases the response to vasopressor agents. Because the drug also interferes with compensatory vasoconstriction, its use is dangerous for patients suffering from shock or recent loss of blood. Neostigmine or bethanechol may be used to combat paralytic ileus.

Dosage.—Hexamethonium chloride, on the basis of comparative molecular weights, provides about one-tenth and one-third more of the cation than the same doses of the bitartrate and bromide salts, respectively. The magnitude of this difference is significant only in the comparative dose of the bromide, particularly when the drug is administered parenterally.

Orally, for hypotensive effect, the average total daily dosage should not exceed 3 Gm.; as much as 4 to 5 Gm. may be tolerated by some patients. For moderate to severe essential hypertension or malignant hypertension, the recommended initial dose is 0.125 Gm. four times daily (total of 0.5 Gm. each day); for patients on salt-free diets or patients who have been subjected to sympathectomy, the initial dose is 0.125 Gm. one or two times daily (total of 0.125 to 0.5 Gm. each day). These dosages may be increased gradually to tolerance. Adequate ganglionic blockade is determined by the presence of the unavoidable side-effects. When this does not lower the blood pressure to the desired level, further increases in dosage are unwarranted. Use of the drug may be continued if it relieves symptoms without further effect on the blood pressure. Reduction in the dosage to eliminate side-effects results in ineffectual ganglionic blockade.

Parenterally, for peripheral vascular disease or for hypotensive effect, a solution of hexamethonium chloride may be injected in single doses of 50 to 100 mg. of the salt, and repeated every six hours as necessary. The maximum dose should seldom exceed 65 mg., but heavy patients may require doses up to 135 mg. For severely ill or debilitated patients, an initial trial dose of 1.3 to 6.5 mg. should be used. This may be gradually increased to tolerance.

Tests and Standards—

Physical Properties: Hexamethonium chloride is a white, crystalline, hygroscopic powder with a faint odor, m.p. 289–292° (with decomposition). It is very soluble in water; soluble in alcohol; and practically insoluble in chloroform and ether. The pH of a 3 per cent solution is 5.0–6.5.

[For more information regarding tests and standards, see *J. A. M. A.*, **151**: 386 (Jan. 31, 1953).]

Dosage Forms of Hexamethonium Chloride

TABLETS. *Identity Tests*: The powdered tablets respond to the identity tests for the active ingredient in the monograph for hexamethonium chloride.

[For more information regarding dosage forms, see *J. A. M. A.*, **151**: 386 (Jan. 31, 1953).]

Warner-Chilcott Laboratories, New York.

Tablets Methium Chloride: 0.125 Gm. and 0.25 Gm.

Insulin Modifications

• • • • • • • • • • • • • *from page 495*

by Peck and Kirtley at Indianapolis General Hospital.

Discussion

There has been a gradual evolution of methods of insulin therapy in the management of diabetes over the last quarter century. The original short-acting insulin requiring multiple daily injections ceased to be the sheet anchor of management with the introduction of protamine zinc insulin, which rapidly became the foundation of treatment, embellished with supplementary doses of unmodified insulin. Clinical experience dictated the next step, via a time-consuming series of comparisons of preparations having all sorts of intermediate timing effects, which led to the conclusion that a preparation having the action characteristics of a 2:1 (protamine zinc insulin:insulin) mixture exerted the most desirable effects for most patients. Then followed a deliberate attempt to produce a preparation, stable and uniform, which could duplicate this action in a practical manner. That this preparation was one that could be prepared in crystalline, highly purified form was undoubtedly fortuitous—NPH insulin crystals happened to exert the desired time action. There is but limited opportunity to change this rate of action except by the addition of required amounts of unmodified insulin to the injection in order to provide a more intense daytime effectiveness.

For the majority of patients the timing of NPH insulin represents the most satisfactory action as measured by minimum number of injections, satisfactory overlap (nocturnal effect), and relative freedom from hypoglycemia. Even in the severe unstable cases some improvement can be anticipated. But it is not a panacea, and it does not change the severe unstable case to a stable one. Such exceptional cases remain difficult individual problems even though management of the bulk of cases is simplified and improved.

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STUDENT BRANCHES

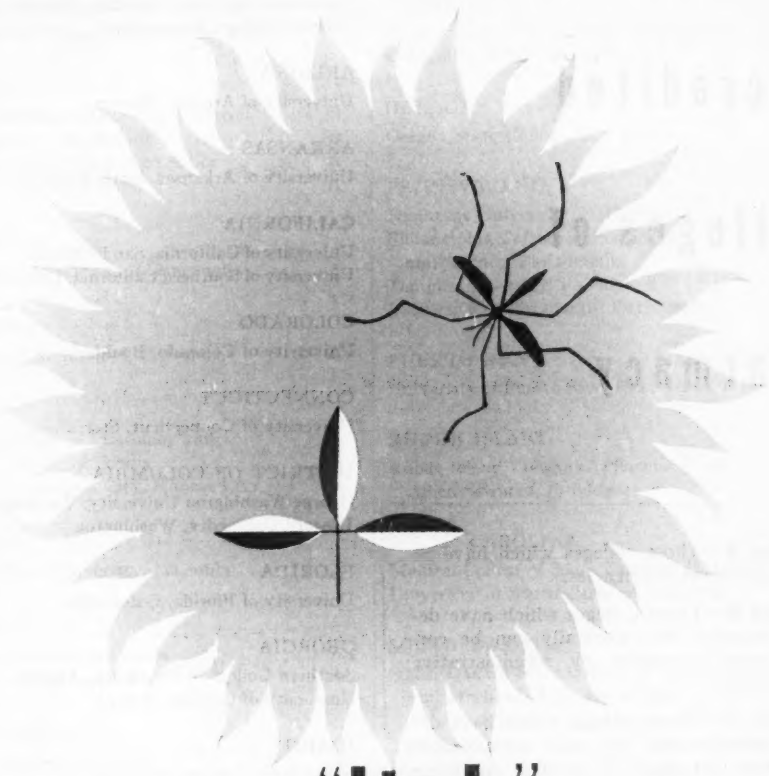
Plans have been made to hold the Districts No. 1 and No. 2 Student Branch Convention of the A.PH.A. at Temple University, Philadelphia, Pa., on May 1, 1954. Advance information can be obtained by contacting Joseph Zdrojewski, president of the **Temple University Student Branch,** Temple University, 3223 N. Broad Street, Philadelphia, Pa.

The new officers for 1953–54 of the **Medical College of Virginia Student Branch** are: Don F. Verne, president; Daniel M. Myers, vice-president; Lloyd J. Kellam, secretary; Harvey B. Morgan, treasurer; and Richard Peatross, historian.

Robert Schwartz is the new president of the **University of Wisconsin Student Branch** for 1953–54. The other officers are: Jerome Stieber, vice-president; Carolyn Ziehm, secretary; and Lyle Block, treasurer.

LOCAL BRANCHES

At the meeting of June 16 of the **Greater Los Angeles Branch** of the A.PH.A., a resolution was passed protesting the passage of H.R. 5740 in its original form and recommending to the members of the Committee on Interstate and Foreign Commerce of the House of Representatives that the bill be amended by the addition of the following section: "Nothing in Section 704 of the Federal Food, Drug and Cosmetic Act as amended (21 U.S.C. sec. 374) shall be construed to apply to a pharmacy or drug store licensed by the board of pharmacy of any state to carry on the compounding and dispensing of drugs, medicines and prescriptions." (See editorial on page 420 of the July 1953 issue of THIS JOURNAL.)



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Class A—Those colleges which have no significant deficiencies.

Class B—Those colleges which have deficiencies that normally can be corrected promptly by administrative action.

Class C—Those colleges which have deficiencies that will take considerable time and effort to correct. A college in this class will be given a reasonable period to be determined by the Council in which to correct its deficiencies or show cause why it should not be dropped from the list of accredited colleges.

Class Y—Newly established colleges which have at least two years of their undergraduate curricula accredited. Accreditation in these instances will be temporary and a college thus accredited will be designated as Y-2 or Y-4 to indicate the number of years of the curriculum which have been accredited. A class Y college which does not apply for full accreditation or one which applies for full accreditation but does not meet all requirements for accreditation as a class A college within one year after the full undergraduate curriculum has been in operation, will be required to show cause why it should not be dropped from the list of accredited colleges.

	Classification
ALABAMA	
Alabama Polytechnic Institute, Auburn	A
Howard College, Birmingham	A
ARIZONA	
University of Arizona, Tucson	A
ARKANSAS	
University of Arkansas, Little Rock	Y-4
CALIFORNIA	
University of California, San Francisco	A
University of Southern California, Los Angeles	A
COLORADO	
University of Colorado, Boulder	A
CONNECTICUT	
University of Connecticut, Storrs	A
DISTRICT OF COLUMBIA	
George Washington University, Washington	A
Howard University, Washington	A
FLORIDA	
University of Florida, Gainesville	A
GEORGIA	
Southern College of Pharmacy, Atlanta	C
University of Georgia, Athens	A
IDAHO	
Idaho State College, Pocatello	A
ILLINOIS	
University of Illinois, Chicago	A
INDIANA	
Butler University, Indianapolis	A
Purdue University, Lafayette	A
IOWA	
Drake University, Des Moines	A
State University of Iowa, Iowa City	A
KANSAS	
University of Kansas, Lawrence	A
KENTUCKY	
University of Kentucky, Louisville	A
LOUISIANA	
Loyola University, New Orleans	A
Xavier University, New Orleans	B
MARYLAND	
University of Maryland, Baltimore	A

	Classification
MASSACHUSETTS	
Massachusetts College of Pharmacy, Boston	A
New England College of Pharmacy, Boston	C
MICHIGAN	
Detroit Institute of Technology, Detroit	B
Ferris Institute, Big Rapids	B
University of Michigan, Ann Arbor	A
Wayne University, Detroit	A
MINNESOTA	
University of Minnesota, Minneapolis	A
MISSISSIPPI	
University of Mississippi, University	A
MISSOURI	
St. Louis College of Pharmacy and Allied Sciences, St. Louis	A
University of Kansas City, Kansas City	A
MONTANA	
Montana State University, Missoula	A
NEBRASKA	
Creighton University, Omaha	A
University of Nebraska, Lincoln	A
NEW JERSEY	
Rutgers University, Newark	A
NEW MEXICO	
University of New Mexico, Albuquerque	A
NEW YORK	
Columbia University, New York	A
Fordham University, New York	A
Long Island University Brooklyn College of Pharmacy, Brooklyn	A
St. John's University, Brooklyn	A
Union University, Albany	A
University of Buffalo, Buffalo	A
NORTH CAROLINA	
University of North Carolina, Chapel Hill	A
NORTH DAKOTA	
North Dakota Agricultural College, Fargo	A
OHIO	
Cincinnati College of Pharmacy, Cincinnati	C
Ohio Northern University, Ada	C
Ohio State University, Columbus	A
University of Toledo, Toledo	A

	Classification
OKLAHOMA	
Southwestern State College, Weatherford	B
University of Oklahoma, Norman	A
OREGON	
Oregon State College, Corvallis	A
PENNSYLVANIA	
Duquesne University, Pittsburgh	A
Philadelphia College of Pharmacy and Science, Philadelphia	A
Temple University, Philadelphia	A
University of Pittsburgh, Pittsburgh	A
PUERTO RICO	
University of Puerto Rico, Rio Piedras, P.R.	A
RHODE ISLAND	
Rhode Island College of Pharmacy and Allied Sciences, Providence	B
SOUTH CAROLINA	
Medical College of South Carolina, Charleston	A
University of South Carolina, Columbia	A
SOUTH DAKOTA	
South Dakota State College of Agriculture and Mechanic Arts, Brookings	A
TENNESSEE	
University of Tennessee, Memphis	A
TEXAS	
Texas Southern University, Houston	A
University of Houston, Houston	A
University of Texas, Austin	A
UTAH	
University of Utah, Salt Lake City	A
VIRGINIA	
Medical College of Virginia, Richmond	A
WASHINGTON	
State College of Washington, Pullman	A
University of Washington, Seattle	A
WEST VIRGINIA	
West Virginia University, Morgantown	A
WISCONSIN	
University of Wisconsin, Madison	A
WYOMING	
University of Wyoming, Laramie	A

Antibacterial Agents• • • • *from page 500*

cases where no preservative would ordinarily be added, as with mercuric and silver salts.

The observed evidences of chemical changes in the 276 solutions tested are indicated in Table II. No mold growth was detected in any solution containing one of the preservatives. Theodore (9) recommends the use of chlorobutanol as a general preservative for ophthalmic solutions. It is noted that phenylethyl alcohol, 0.5 per cent, showed no reaction with any tested medicinal agent that would require a preservative. Results of a bacteriological study (12) show that *Pseudomonas aeruginosa* cultures that were added to the solutions containing phenylethyl alcohol, 0.5 per cent, did not survive. If the results of planned clinical tests with solutions containing phenylethyl alcohol are favorable, it would appear that this is an excellent antibacterial preservative that can be used in stock vehicles for compounded ophthalmic solutions. The data given in Tables I and II, indicate certain incompatibilities with chemical preservatives, and they can be used as a selective guide in the choice of an antibacterial agent.

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Author's Summary

Reports by physicians and bacteriologists have indicated the dangerous possibilities of infection, re-infection, and cross-infection in the treatment of eye conditions with contaminated or preservative-free ophthalmic solutions.

The Federal Food and Drug Administration has ruled that manufactured or repacked ophthalmic solutions must be sterile.

The first step in the educational phase of the proposed modification of the "generally accepted" practice of compounding ophthalmic solutions can be an agreement with physicians to add an antibacterial agent to the prescribed ingredients.

Compatibility studies of antibacterial agents and substances prescribed in ophthalmic solutions are reported.

TABLE II.—EFFECTS OF CHEMICAL PRESERVATIVES OBSERVED IN SOME SOLUTIONS[a]

Medicinal Agent Added to Solution of Preservative	Concn., %	Preservative in Aqueous Vehicle: Phenol, 0.5%	Chlorobutanol, 0.5%	Benzalkonium Chloride, 1:5,000	Thimerosal, 1:20,000	Me. Paraben, 0.18%; Pr. Paraben, 0.02%	Phenylethyl Alc., 0.5%	Distd. Water
Dextrose	5.6	...	...	sl. P	...	...	...	Mold
Mercuric Chloride	1.0	P	...	T	P	P	sl. P	Clear
Mercuric Succinimide	1.0	...	...	...	P	...	...	Clear
Phenobarbital Sodium	1.0	...	P(c)	...	...	P(c)	...	Clear
Physostigmine Salicylate (with 1% sodium bisulfite)	0.5	...	...	T	...	...	...	Clear
Potassium Iodide	1.4	...	...	sl. T	...	...	...	Clear
Silver Nitrate	1.0	sl. P	sl. T	P(b) S(y)	P(y)	...	sl. P	Clear
Sodium Borate	1.0	...	...	T	...	...	...	Clear
Sodium Nitrate	1.5	...	...	P(c)	...	...	...	Clear
Sodium Sulfadiazine	5.0	P S(y)	P	P	P(c)	P	...	Clear
Sodium Sulfathiazole	5.0	P(c) S(y)	P(c)	P(b)	sl. P	P	...	Clear

P = precipitate, S = solution, T = turbidity, (b) = brown, (c) = crystalline, (y) = yellow, sl. = slight.
[a] The solutions were observed for at least one month at room temperature.

BRIEFLY NOTED

COLLEGES

Dr. Louis Delwin King has been recently appointed to the faculty of the **Rutgers University** College of Pharmacy as assistant professor of Pharmacy. Dr. King received the B.S. in Pharmacy from the University of South Carolina in 1949, the M.S. in Pharmacy and the Ph.D. degree from the University of Florida where he has been a teaching assistant. He is a member of Kappa Psi and Rho Chi, professional fraternities, and a member of the AMERICAN PHARMACEUTICAL ASSOCIATION.

Clement P. Becker, sales manager for McKesson & Robbins' Newark division, has been elected chairman of the Planning Committee of **Rutgers University's** 1954 Pharmaceutical Conference. Re-elected executive secretary of the Committee was Louis E. Kazin, associate editor of *Drug Topics* and *Drug Trade News*, formerly director of Rutgers' Pharmaceutical Extension Service. Elected vice-chairman was John L. Voigt, newly appointed successor to Mr. Kazin at Rutgers.

Dean Glenn L. Jenkins of the Purdue School of Pharmacy has recently announced that the 1953 Purdue Druggists' Business Conference will be held on the campus of **Purdue University** on Thursday, October 29, 1953. Among the topics of interest to the progressive pharmacist that will be discussed at this Conference are: "What to Do with the Soda Fountain?" which will be discussed by two pharmacy owners—one will tell why he took out his soda fountain and the results of his doing so, and the other, why he does not intend to take out his soda fountain; "Cooperative Advertising," and "How to Create Good Community Relations." A complete program of the Conference may be obtained by writing: Pharmacy Extension Department, Purdue University School of Pharmacy, Lafayette, Ind.

Several assistantships and fellowships are available at the **University of Florida,** College of Pharmacy, it has been announced by the College. One-third graduate assistantships require 15 hours departmental work per week, and half-time graduate assistantships require 20 hours per week of the student's time. The remainder is devoted to graduate study. Research Fellows devote full time to graduate work.

A three-year development program for the **University of Southern California** School of Pharmacy has been started and will be completed on the School's 50th Anniversary. Funds will be used for equipment, scholarships, and professorships to maintain the reputation of the School of Pharmacy.

A new products formulation laboratory has been set up at the **University of Connecticut** that permits pharmacy students to understand the problems of the manufacturer and follow a formula from the time it is created until it reaches the pharmacy counter. More than that, the University laboratory is being developed to train personnel for careers in the nation's pharmaceutical laboratories. Production development in drug manufacturing, according to Pharmacy Dean H. G. Hewitt, is both an art and a science.

The graduate course in product formulation and the laboratory itself is under the direction of Dr. Donald M. Skauen, associate professor of Pharmacy.

Dean Harold G. Hewitt presented one Doctor of Philosophy degree, three Master of Science degrees and 54 Bachelor of Science degrees in pharmacy at the 70th Annual Commencement of the **University of Connecticut.** The Commencement marked the 28th year of the College of Pharmacy.

The 116th Commencement of the **Medical College of Virginia** was held on June 2 with 334 in the graduating classes: 100 in medicine, 50 in dentistry, 56 in pharmacy, 57 in nursing, 39 in physical therapy, 7 in hospital administration, 19 in medical technology and 6 Master of Science degrees—4 in biochemistry, 1 in biology and 1 in legal medicine.

(Continued on next page)

Colleges

• • • • • • • • • *from preceding page*

Thirty-four students graduated from the College of Pharmacy, **University of Arizona,** on May 27 with the degree of Bachelor of Science in Pharmacy. The faculty held a reception in honor of the graduates and their parents that afternoon.

Mr. Louis H. Pink, former president and chairman of the Board of the Associated Hospital Service of New York, and former Superintendent of Insurance of New York State, gave the graduation address at the 1953 commencement exercises of **Brooklyn College of Pharmacy** on June 9. There were 118 graduates, of which one received his degree of Magna Cum Laude and 13 received their degrees of Cum Laude.

The George Washington University has received two grants, totaling $10,250, for medical research into the value and effectiveness of certain vaccines and drugs used in combating infant and childhood diseases. The grants for $4,250 and $6,000 were made by Eli Lilly and Co.

The University has also received $21,271, for studying the effects of aureomycin, terramycin, and penicillin on cancer when they are used in conjunction with mustard drugs and X-ray treatments. These grants, made by Lederle Laboratories Division of American Cyanamid Company and The Chas. Pfizer Company, were for $12,000 and $9,271, respectively.

Creighton University College of Pharmacy is celebrating the 75th anniversary of its founding this year.

ASSOCIATIONS

The American Heart Association has marked its Fifth Anniversary as a voluntary health agency by awarding, jointly with its affiliates, an additional $473,930.59 for 89 research grants-in-aid in the field of heart and blood vessel diseases, it was announced recently by Dr. Robert L. King, president of the Association. The newly approved grants-in-aid were made possible by public contributions to the 1952 Heart Fund campaign, Dr. King said. He also noted that the latest awards increase to a grand total of almost six and a half million dollars the sums spent for research studies by the American Heart Association and its affiliated state and local associations over the five-year period.

The Alpha Omicron Chapter of the **Rho Chi Society** of the University of Pittsburgh School of Pharmacy recently installed in the Farmers Bank Building in Pittsburgh, Pa., a display commemorating 75 years of service to pharmaceutical education.

The Board of Pharmacy of the State of New Jersey has promulgated a regulation that "No prescription blank shall bear the imprint thereon of the name of any pharmacy or drug store or other licensed premises or bear the name or address of any person registered under this statue." Stephen M. Duschock, president of the Board, indicated that all pharmacy owners were informed of this new regulation in the letter accompanying pharmacy permits for the fiscal year which began on July 1, 1953. This regulation will not become effective, however, until July 1, 1954, to give physicians an opportunity to use up blanks already printed. Mr. Duschock said that this regulation was adopted by the Board at the request of the Board of Trustees of the New Jersey Pharmaceutical Association.

The 124 interns working in as many pharmacies obtaining experience for a New Jersey pharmacist certificate have recently completed a second prescription survey required by the **New Jersey Board of Pharmacy** to be made by all interns. Mr. W. E. Powers, the secretary of the Board, has disclosed that out of 62,538 new prescriptions surveyed, there were only 5 requiring the pharmacist to make pills extemporaneously, only 43 for tablet triturates manufactured by the pharmacist, and only 104 for suppositories. He also indicated that 26.4 per cent of all of the prescriptions required some compounding.

The Indiana Pharmaceutical Association held its 72nd Annual Convention at the Claypool Hotel, Indianapolis, Ind., June 16 to 18. A. T. Ehrhardt, Kokomo, was elected president of the Association, succeeding Byron Childress of Mishawaka. Other officers are: J. B. Lischke, Lafayette, first vice-president; Wally Sielski, Gary, second vice-president; and Thurman Miller, Terre Haute, third vice-president. Joseph B. Wade was reappointed treasurer, and Henry W. Heine, executive secretary.

The **Cleveland Alumni Chapter of the Rho Pi Phi** International Pharmaceutical Frater-

nity was host for the 29th Annual Convention with headquarters at the Hotel Statler on August 2–5. Delegates and fraters attended from throughout the States and Canada. William Gross is chairman of the Convention.

The second edition of the "Inventory of Social and Economic Research in Health," containing concise details of about 250 research projects throughout the nation dealing with social and economic aspects of health, has just been published by **Health Information Foundation.**

Alpha Zeta Omega Pharmaceutical Fraternity held its 33rd annual Convention at the William Penn Hotel in Pittsburgh, July 19–22. "Mu" Chapter of the University of Pittsburgh and the Pittsburgh Alumni Chapter were hosts. A highlight of the Convention was the Pharmaceutical Forum on Tuesday afternoon, July 21.

Newly elected officers of the **Rho Chi Chapter,** at the University of Mississippi, are: Dr. W. Lewis Nobles, president; Walter J. Pierron, Jr., vice-president; and Professor W. W. Johnson, secretary-treasurer.

MANUFACTURERS

Establishment of the **Mathieson-Squibb Institute of Chemical Research and Engineering** has been recently announced by Thomas S. Nichols, president of the Mathieson Chemical Corporation. The president of the newly created Institute will be Dr. Carl F. Prutton, vice-president of the Mathieson Chemical Corporation. The new organization will consolidate Mathieson's expanding chemical research and engineering functions.

Lederle Laboratories Division, American Cyanamid Company, has opened a new branch office in Portland, Ore. The new office is located at 3030 Northwest 29th Avenue, and will serve as Lederle's headquarters in the Pacific Northwest, replacing the Division's Seattle, Wash., office. Mr. Kenneth H. Tate is branch manager; E. L. Larson, regional sales manager; Everett Howe, assistant regional sales manager.

For the first time, a husband- and -wife team of scientists are the recipients of the Ciba Award for distinguished research in endocrinology, it was announced recently by officials of

(Continued on page 528)

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• • • • • • • • • • • • *from page 527*

the Endocrine Society and **Ciba Pharmaceutical Products, Inc.**

The recipients, Dr. Sidney Roberts, associate professor of Physiological Chemistry at the School of Medicine, University of California, and his wife, Dr. Clara Marion Szego, assistant professor of Zoology at the same university, received the Ciba Award of 1953 at the 35th Annual Meeting of the Endocrine Society.

Cutter Laboratories has announced that its production of Dextran is now sufficient to meet the needs of both the Armed Forces and civilian hospitals. In order to fulfill its government contract and, at the same time, supply the civilian hospital demand for the plasma extender, a revolutionary photo electric Dextran filling machine was designed and built by Cutter engineers at the Berkeley plant.

Mr. Harold C. Baker has resigned as vice-president of the **Fischer-Stevens Service, Inc.** Mr. Baker has been affiliated with Fisher-Stevens for more than 30 years, and has been retained as a sales consultant.

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No. 8

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PUBLISHED by the American Pharmaceutical Association. Publication Office: 20th and Northampton Streets, Easton, Pa. Editorial office (and address for all correspondence): 2215 Constitution Ave., N.W., Washington 7, D. C.

ANNUAL SUBSCRIPTION—Journal of the American Pharmaceutical Association complete (both editions): United States and Pan American $7; Canada $7.70; other foreign $8; members of the American Pharmaceutical Association with dues, $4. Each edition, Scientific Edition or Practical Pharmacy Edition: United States and Pan American $4; Canada $4.35; other foreign $4.50. Single numbers, either edition: United States and Pan American $0.35; Canada $0.40; other foreign $0.50.

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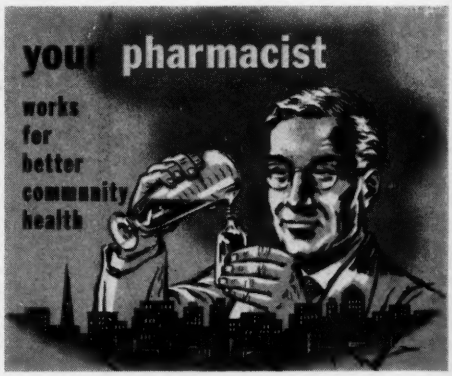
ENTERED as second-class matter January 23, 1917, at the Post Office at Easton, Pennsylvania, under the act of March 3, 1879, as 24 times a year; Scientific Edition monthly on the 5th; Practical Pharmacy Edition monthly on the 20th. Acceptance for mailing at a special rate of postage provided for in Section 1103, Act of October 3, 1917, authorized July 10, 1918.



Plans for National Pharmacy Week, October 4–10, are going forward rapidly, according to B. R. Mull, chairman of the Committee on Public Relations of the AMERICAN PHARMACEUTICAL ASSOCIATION, sponsors of the Week. The Committee is now distributing special kits to retailers; a window streamer and the rules for the window display competition have been mailed to every pharmacy in the country. The complete rules appeared in the August issue of THIS JOURNAL, pages 489–493.

In addition to the material sent to pharmacies, the Committee has also prepared a special television slide film. This slide will be mailed in mid-September to every television station in the country. It carries the message "Your Pharmacist Works for Better Community Health," the theme of National Pharmacy Week. However, the Committee pointed out that the slide can be used after National Pharmacy Week as well, since it does not carry the dates of this year's observance. Every month the Committee will send new text to be read by the station personnel as the slide is shown. Thus, in the months to come, the stations will be able to use the same slide for other public health messages. The slide film, mailed to over 300 television stations in all sections of the country, is shown above.

"Our emphasis," Mr. Mull stated, in discussing the slide, "is initially on National Pharmacy Week, and the stations will have copy which pays tribute to the pharmacist, for use during the period October 4–10. However, after the Week is over, they can keep the slide on file and use it time after time with new health messages that we will provide. By so doing, we will bring the pharmacist's message of public health to the attention of the public all year, and not merely during the one important week designated as National Pharmacy Week."

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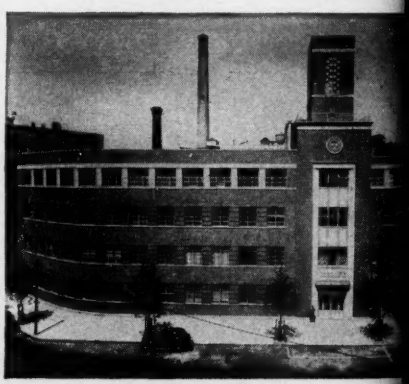
This is only the beginning. The medical uses of hormones are growing daily. Products now in research, in pilot plant production, and on trial in the leading medical centers of the world are on the eve of sales introduction. The Pfizer Syntex line of steroid hormone preparations is another opportunity for new volume, new profits in one of the most rapidly expanding fields of prescription business today.



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RECENT

PROGRESS IN MEDICINE

American Dental Association Urges Conservative Attitude on New "Anti-enzyme" Dentifrices

The American Dental Association has urged both the dental profession and the public to adopt "a conservative attitude" toward actual or implied claims for anti-decay qualities of anti-enzyme toothpastes. The warning came in a special new release issued prior to the introduction of the first of these new dentifrices.

The Association's Council on Dental Therapeutics and the Council on Dental Research, in a joint statement, reported that they had been unable to find any evidence that the new dentifrices have been directly demonstrated to reduce the incidence of dental decay in humans.

"It is the opinion of the councils, therefore, that on the basis of the evidence presently available, actual or implied claims of anti-decay qualities for the new dentifrices are premature," the joint statement said.

Pointing out that the evidence so far consists of laboratory findings only, the two councils said that it is "contrary to the public interest" to suggest that the use of any dentifrice may be substituted for well-recognized dental health procedures such as toothbrushing immediately following the eating of sugar products and the avoidance of excessive consumption of sugar-containing preparations.

The American Dental Association's Councils' report indicates the following conclusions:

"Some information indicates that the advertising (of the anti-enzyme toothpastes) may suggest to the casual reader that the products' effectiveness in preventing dental decay is such that standard dental health procedures can be disregarded by the individual using the dentifrice. Technical statements may lead the reader to infer that adequate tests have demonstrated the validity of this assumption.

"In order to provide the dental profession and the public with proper information in this matter, the Council on Dental Research and the Council on Dental Therapeutics of the American Dental Association have attempted to ascertain the basis for the claimed effectiveness of these new dentifrices.

"It is the opinion of the councils that all preparations designed to reduce the incidence of dental decay in humans should be evaluated by direct clinical measurements. Anti-decay claims are not justified for products until their effect in actually reducing human dental caries has been directly demonstrated by acceptable controlled studies of human population groups. The councils have not been able to obtain any evidence that clinical data are available to substantiate such claims for the new dentifrices. The only available report is based upon laboratory findings.

"It is the opinion of the councils, therefore, that on the basis of the evidence presently available, actual or implied claims of anti-decay qualities for the new dentifrices are premature.

"It is the further opinion of the councils that it is contrary to the public interest to suggest that the use of any dentifrice may be substituted for well-recognized dental health procedures.

"The councils continue to advise all individuals to avoid excessive consumption of sugar-

(Continued on page 536)

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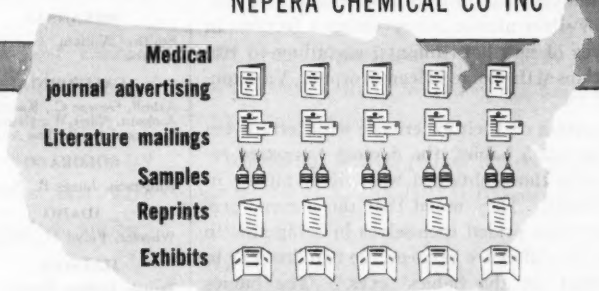

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Antibiotics & Chemotherapy, 3:299, March, 1953.

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"BIOMYDRIN" is a trademark of Nepera Chemical Co., Inc.

Recent Progress

• • • • • • • • • • • • *from page 534*

containing preparations which have been demonstrated to be related to the development of carious lesions.

"The councils believe also that presently available evidence indicates that conscientious toothbrushing immediately following the ingestion of sugar products should continue to be recommended as an individual procedure to reduce dental caries.

"In summary, the councils suggest that both the dental profession and the public adopt a conservative attitude toward any new product for which therapeutic claims have not been conclusively demonstrated by acceptable controlled clinical studies."

(Joint Statement by Councils on Dental Research and on Dental Therapeutics, *J. A. D. A.*, **47:** 349, Sept., 1953.)

Terramycin Ointment for Eyes of Newborn

Terramycin has proved a satisfactory substitute for silver nitrate in preventing infections in the eyes of new-born infants, according to two physicians at the Sacred Heart Hospital, Yankton, S. D.

Reporting on their experience with terramycin used on 1,225 babies, the doctors compared results with those obtained with silver nitrate in 175 infants. They noted that the nursery personnel "soon prided themselves in being able to notice the difference between the two drugs as to the effect on the babies' eyes." The babies treated with silver nitrate had reddened conjunctiva and kept their eyes closed for three to four days. The eyes of the terramycin-treated babies, were bright, open, and the conjunctiva were clear.

Since eye infections in the new-born are most frequently caused by gonococci and pneumococci encountered when the baby passes through the mother's birth canal, silver nitrate and penicillin have both been used routinely as prophylactic agents. Both are potent killers of these germs. However, penicillin ointments have been criticized for causing sensitivity reactions in a number of patients and the American Medical Association recently withdrew its approval of such products.

The physicians concluded that "Terramycin is satisfactory to use in place of silver nitrate." The drug is active against the gonococcus, non irritating to the eyes, and, in the ointment form, has a low index of sensitivity reactions.

(Willcookson, T. H., and Cox, C. D., *S. D. Jrl. Med. & Pharm.*, **6:** 147, June, 1953.)

New A.Ph.A. Members

NEW LIFE MEMBERS

Boncivino, Alfred, Cambria Heights, L. I., N. Y.

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Cameron, R. Becton, Phoenix
Phelps, Arthur L., Phoenix

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Palkovacs, Barney B., Chillicothe

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Johnson, Charles E., Salt Lake City
Pinborough, John V., Salt Lake City
Silvers, Dave R., Salt Lake City
Stauffer, J. C., Hyrum

VIRGINIA

Brown, Terry D., Lynchburg

Deceased Members

Blanchard, Roger A., New Orleans, La.
Crowe, Robert Latta, Memphis, Tenn., July 26, 1953
Fisk, Frank Byron, Tarrytown, N. Y., July 10, 1953
Goldstein, Dave, Birmingham, Ala.
Koscho, Stephen, Eynon, Pa., April 14, 1953
Lohrberg, Rowland O., Philadelphia, Pa., July 21, 1953
Peterson, Ivan, Montrose, Calif., June 12, 1953
Rupp, Walding C., Toledo, Ohio, July 27, 1953 (Life Member)
Wickham, Anthony Emile, Seaside Park, N. J., July 27, 1953

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℞ information service

Members of the American Pharmaceutical Association are invited to submit their professional problems to The Journal, 2215 Constitution Ave., N. W., Washington 7, D. C., giving all pertinent details.

Ethyl Vanillate

Would you please supply us with some information concerning ethyl vanillate, a drug used in histoplasmosis.—H. B. G., Washington, D.C.

Ethyl vanillate, $C_{10}H_{12}O_4$ (ethyl-4-hydroxy-3-methoxybenzoate), is prepared from vanillic acid which is prepared by sulfite treatment of wood pulp. It can be obtained from the Sulphite Products Corp. and Celanese Corp. of America. It is toxic toward many types of microorganisms, especially fungi.

Ethyl vanillate, 20 mg. per 100 cc., inhibits growth of *Histoplasma capsulatum*. Dosage varies from case to case. One case started with 0.62 Gm./Kg. of body weight per day in divided doses; later increased to 1.25 Gm./Kg. and then to 1.55 Gm./Kg. per day. This dosage was continued for 47 days. The margin between therapeutic and toxic levels is only about 25 to 30 per cent. [Christie, J. G., *Pediatrics*, **7:** 7 (Jan., 1951); through *J. A. M. A.*, **146:** 215 (May 12, 1951).]

Coal Tar, Sulfur, and Salicylic Acid Ointment, Greaseless

If available, please furnish information about a formula for coal tar, sulfur, salicylic acid in a greaseless ointment base, together with the method of compounding. If a formula using other than crude coal tar in this type of preparation is available, please furnish it as well; that is, a derivative or distillate of tar.—R. D. S., Staten Island, N.Y.

Coal tar, sulfur, and salicylic acid can be incorporated in a vanishing cream, or a water-washable base such as the Hydrophilic Ointment of the U.S.P. A somewhat similar base, proposed by Beeler, is composed of cetyl alcohol, 15 per cent; white wax, 1 per cent; sodium lauryl sulfate, 2 per cent; propylene glycol, 10 per cent; and water, 72 per cent. The propylene glycol is dissolved in the oil phase and the oily mixture, which is at about 70° C., is added to the water phase containing the emulsifier (sodium lauryl sulfate) at the same temperature, and the mixture is stirred occasionally until it reaches room temperature. The concentration of the coal tar should be decreased to about one-fifth the amount you would incorporate into a grease base.

The following formula for a "Stainless Coal Tar Ointment" appears in *Drug Standards*, **21:** 150 (July-Aug., 1953):

Coal Tar Solution	50.0
Polyethylene Glycol 400 Monostearate	250.0
Polyethylene Glycol Ointment, U.S.P.	700.0
Menthol	2.0

Mix thoroughly the polyethylene glycol 400 monostearate and the polyethylene glycol ointment. Dissolve the menthol in the coal tar solution; add the solution in small portions to the mixture, with mulling or trituration after each addition.

Sulfur and salicylic acid (no more than 5 per cent of salicylic acid) can be incorporated in the same base.

Calamine Lotion

As a member of the United States Marine Corps, I have been assigned the job of pharmacist in a Naval dispensary. And since I am anticipating an increased need for Calamine Lotion, I would appreciate any information you might have that would help me make a more elegant and efficacious lotion. I would appreciate also, information that would aid me in securing the following new suspending agents—CMC-M and Aerosol OT. I have read the article by S. W. Goldstein in the April, 1952, issue of THIS JOURNAL.*—A. J. R., Quantico, Va.*

The official Calamine Lotion would be prepared by the formula and procedure given in the U.S.P. XIV. You could prepare the lotion according to the formula and directions given in the article referred to above and label it Calamine Lotion, Modified. In order to obtain the best results with the modified lotion, we would suggest that you state on the label: "Use Sparingly." Most comfortable application and use are obtained when the modified lotion is applied as a thin film.

If you plan to make large amounts of the Lotion, you can order Sodium Carboxymethyl-

(Continued on page 540)

AMES
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NEW pleasant, refreshing relief in "common colds"

APAMIDE-VES
TRADEMARK

(Buffered N-acetyl-p-aminophenol, *Ames*, in Citrate-Carbonate Effervescent Base)

NEW EFFERVESCING ANALGESIC • ANTIPYRETIC

The prompt, prolonged, *prescribed* relief provided by effervescing *Apamide-Ves* appeals to both physician and patient... promises *profitable prescription volume business for you.*

- **acts more rapidly; ready for immediate absorption**
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- **provides protective alkaline factor**
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- **delightful to take**

Apamide-Ves is prescribed for the many patients requiring relief of pain and reduction of fever in respiratory infections, functional headache, muscular or joint pain, dysmenorrhea, and dental pain.

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A comprehensive promotion of *Apamide-Ves* is reaching every physician in your neighborhood. We suggest that you stock an adequate supply of *Apamide-Ves* from your wholesaler... *now.*

Apamide-Ves Tablets: Effervescing analgesic-antipyretic; individually foil-wrapped; packages of 50.

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Rx Information

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cellulose—Medium Viscosity, Pharmaceutical Grade, from the Hercules Powder Co., Wilmington, Del. Aerosol OT (Dioctyl Sodium Sulfosuccinate, N.F.) can be ordered from the American Cyanamid and Chemicals Co., 30 Rockefeller Plaza, New York 20, N.Y.

Both of these materials can be ordered in small lots from the R. F. Revson Co., 243 W. 17th St., New York 11, N.Y.

If the modified product is to be run through a colloid mill or homogenizer, you might reduce the sodium CMC-M content from 2 per cent to about 1.8 per cent.

Other articles in which formulas for Calamine Lotion are discussed appeared in the May, 1953, issue of THIS JOURNAL.

Eserine Salicylate Ophthalmic Solution

Can you suggest a formula for an ophthalmic solution containing eserine salicylate 1/4 or 1/2 per cent? This is to be a sterile, isotonic, and buffered solution which will not exhibit the usual eserine decomposition color changes.—S. B., Montreal, Canada.

The following formula is based on the report of H. W. Hind, F. M. Goyan, and T. W. Schwarz, *J.A.Ph.A., Sci. Ed.*, **36:** 413 (1947).

Eserine Salicylate Ophthalmic Solution	0.5%
Eserine Salicylate	0.5
Sodium Sulfite	0.1
Distilled Water	17.0
Phenylmercuric Nitrate	1:100,000
Boric Acid Buffer Solution, pH 5, *q.s.*	100.0

The buffer solution contains boric acid 22 Gm. in enough distilled water to make 1,000.0 cc. Phenylmercuric nitrate, 0.01 Gm., can be included in each 1,000.0 cc. of the buffer solution to obtain a 1:100,000 solution of the preservative in that solution.

Sodium sulfite retards the development of colored compounds in solutions containing eserine.

The solution can be sterilized by the procedure for Sterilization by Filtration as described under Methods of Sterilization of Parenteral Injections in the *British Pharmacopoeia 1953*, pages 848–849. In the case of small lot production, the method and equipment described by F. H. Theodore and R. R. Feinstein, *Am. J. Ophthalmology*, **35:** 656 (May, 1952), can be employed.

For Full Formula Antianemia Therapy

FERGON® PLUS *Capsules*
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A POWERFUL PLUS in THERAPY and SALES

PLUS—because they are full formulas of antianemic and nutritional factors.

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Fergon Plus Capsules contain well tolerated ferrous gluconate with vitamin B_{12}, folic acid, liver, gastric mucosa and vitamin C.

Delicious Fergon Compound Elixir contains ferrous gluconate, vitamin B_{12}, vitamin B_1, vitamin B_2, and vitamin B_6, folic acid, nicotinamide and pantothenic acid.

Get that EXTRA SALES PLUS
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Introducing

Daprisal*

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a potent new non-narcotic analgesic preparation containing the components of Dexamyl†

'Daprisal' has 2 beneficial effects on the patient in pain:

It relieves the physical aspects of pain through the potentiation of its acetylsalicylic acid and phenacetin components by amobarbital.

It relieves the psychic aspects of pain because it contains the components of 'Dexamyl'—Dexedrine‡ and amobarbital.

Harris and Worley evaluate 'Daprisal' as "... the first non-narcotic ever tested in this laboratory which caused a statistically significant elevation of the threshold to experimentally induced pain." (Presented before the Illinois Section of the Soc. Exper. Biol. & Med., May 26, 1953.)

FORMULA: Each 'Daprisal' tablet contains: 'Dexedrine' Sulfate (dextro-amphetamine sulfate, S.K.F.), 5 mg.; amobarbital (Lilly), ½ gr.; acetylsalicylic acid, 2½ gr.; phenacetin, 2½ gr.

AVAILABLE: 'Daprisal' is available—on prescription only—as follows:

PACKAGE SIZE	PRICE TO RETAILER
Bottles of 50 tablets	$1.94 each

So that you can meet the demand for 'Daprisal', order an adequate supply from your wholesaler now.

Smith, Kline & French Laboratories, Philadelphia

*Trademark †T.M. Reg. U.S. Pat. Off.
‡T.M. Reg. U.S. Pat. Off. for dextro-amphetamine sulfate, S.K.F.

NEW PRESCRIPTION PRODUCTS

ADRENOSEM—AMPULS AND TABLETS

Description: Each ampul contains 5 mg. of Andrenosem (adrenochrome monosemicarbazone sodium salicylate complex); each sugar-coated, orange tablet contains 1 mg. of Adrenosem.

Indications: For the treatment of conditions characterized by increased capillary fragility and permeability; also indicated for idiopathic purpura, retinal hemorrhage, familial telangiectasia, surgery, epistaxis, and hemoptysis.

Administration: In mild, low-grade bleeding, the recommended dosage is one ampul intramuscularly every three or four hours until bleeding is controlled; then one tablet orally four or five times daily until bleeding stops. For active bleeding, one ampul intramuscularly every two hours until controlled. The frequency of dose is then diminished.

Form Supplied: Ampuls—packages of 5 and 25; Tablets—bottles of 50.

Source: The S. E. Massengill Company, Bristol, Tenn.

AMSUSTAIN TABLETS—TWO DOSAGE FORMS

Description: Tablets containing 15 mg. and $7^1/_2$ mg. dextro-amphetamine sulfate.

Indications: Recommended as a mood agent, for the treatment of obesity, and as an adjunct for the treatment of alcoholism.

Administration: As prescribed by physician.

Form Supplied: Bottles of 30 and 500 tablets.

Source: The Key Corporation, Miami, Fla.

CLISTIN

Description: Each pink, scored tablet contains 4 mg. of Clistin Maleate, 2-[*p*-chloro-alpha-(2-dimethylaminoethoxy) benzyl] pyridine maleate.

Indications: For the symptomatic treatment of allergic conditions; also as adjunctive therapy in bronchial asthma.

Administration: As directed by physician.

Form Supplied: Bottles of 100 and 1,000 tablets.

Source: McNeil Laboratories, Inc., Philadelphia, Pa.

CO-ELORINE

Description: Each capsule contains Elorine Sulfate (1-cyclohexyl-1-phenyl-3-pyrrolidino-1-propanol methsulfate), 25 mg., and amobarbital, 8 mg.

Indications: For the relief of spasm and gastrointestinal hypermotility and as an adjunct in the treatment of peptic ulcer. Especially useful in those conditions aggravated by nervous tensions, such as pylorospasm, peptic ulcer, gastritis, irritable colon, spastic colitis, mucous colitis, regional ileitis, and ulcerative colitis.

Administration: Average adult dose is one or two capsules three or four times daily.

Form Supplied: Bottles of 100 and 1,000.

Source: Eli Lilly and Company, Indianapolis, Ind.

CORTEF ACETATE OINTMENT

Description: Ointment containing Cortef (hydrocortisone-compound F) acetate, 25 mg. per Gm. ($2^1/_2$ per cent), or 10 mg. per Gm. (1 per cent) in a bland, nonirritating base.

Indications: For treatment of contact dermatitis, pruritus ani and vulvae, atopic dermatitis, neurodermatitis, and seborrheic dermatitis.

Administration: After initial cleansing, a small amount of Cortef Acetate Ointment is rubbed gently into the involved area one to three times a day. Applications may be reduced to one every two to three days for maintenance, if required.

Form Supplied: 5-Gm. tubes of 1 per cent and $2^1/_2$ per cent ointment.

Source: The Upjohn Company, Kalamazoo, Mich.

DAPRISAL TABLETS

Description: Each tablet contains: dextro-amphetamine sulfate, 5 mg.; amobarbital, $^1/_2$ gr.; acetylsalicylic acid, $2^1/_2$ gr.; and phenacetin, $2^1/_2$ gr.

Indications: For the relief of pain and the depression, nervous tension, and anxiety that intensify and prolong pain perception. Daprisal should not be used in patients hypersensitive to sympathomimetic compounds or barbiturates, or in cases of coronary or cardiovascular disease in which vasoconstrictors are contraindicated. Use with caution in the presence of marked hypertension.

(Continued on next page)

Administration: One tablet every three hours as needed.

Form Supplied: Bottles of 50 tablets (on prescription only).

Source: Smith, Kline & French Laboratories, Philadelphia, Pa.

SOLUTION DORSACAINE HYDROCHLORIDE

Description: Solution containing 0.4 per cent of 2-diethylaminoethyl-4-amino-3-butoxybenzoate hydrochloride in sterile, isotonic sodium chloride solution.

Indications: For the rapid induction of anesthesia for tonometry, gonioscopy, and short operative procedures on the eye requiring anesthesia.

Administration: As directed by physician.

Form Supplied: Bottles of 1/2 oz. and 2 oz.

Source: Smith-Dorsey, Division of The Wander Company, Lincoln, Neb.

ELORINE SULFATE

Description: Capsules containing either 25 mg. or 50 mg. of Elorine Sulfate—a quaternary ammonium compound described chemically as 1-cyclohexyl-1-phenyl-3-pyrrolidino-1-propanol methsulfate.

Indications: For the treatment of functional and organic conditions in which spasm of the gastrointestinal tract is a prominent factor. Elorine Sulfate should be avoided in those conditions in which inhibition of the parasympathetic nervous system is undesirable, such as glaucoma; and used with caution in cases of tachycardia and urine retention.

Administration: Oral dosage of 50 mg. every six hours is recommended as an average (25–100 mg.). The frequency of administration may be altered, generally within the limits of four and eight hours.

Form Supplied: Both size capsules (25 mg. and 50 mg.) in bottles of 100 and 1,000.

Source: Eli Lilly and Company, Indianapolis, Ind.

ERYTHROSULFA TABLETS

Description: Each yellow, coated tablet contains: erythromycin, 100 mg.; sulfadiazine, 83 mg.; sulfamerazine, 83 mg.; and sulfamethazine, 83 mg.

Indications: For the treatment of pneumoccic, staphylococcic and streptococcic infections, particularly in individuals sensitive to the other antibiotics and in infections caused by organisms resistant to other antibiotics—such as pharyngitis, tonsillitis, scarlet fever, pneumonia, septicemia, pyoderma, enteritis, otitis media, and sinusitis.

Administration: Average dosage is two tablets every six hours, continued for 48 hours after all evidence of infection has disappeared. In severe infections the dosage may be increased to four tablets every six hours.

Form supplied: Bottles of 50 tablets.

Source: The Upjohn Company, Kalamazoo, Mich.

MALCOTRAN

Description: Each uncoated, scored tablet contains 10 mg. of homatropine methylbromide.

Indications: For use as an anticholinergic and ganglionic blocking agent; it relieves peptic ulcer symptoms and also reduces free acidity, total acidity, and volume of gastric juice. It also suppresses hypermotility of the large and small intestine, as well as of the stomach.

Administration: Recommended starting dosage is one or two tablets q.i.d. with adjustments as may be indicated for individual patients.

Form Supplied: Bottles of 100, 500, and 1,000 tablets.

Source: Maltbie Laboratories, Inc., Newark, N.J.

PYMADEX—TABLETS AND INJECTION

Description: Each cc. of injection and each scored tablet contains: pyranisamine maleate, 25 mg., and dextro-amphetamine hydrochloride, 2 mg.

Indications: For use as an antihistaminic agent in various allergic entities, and as an antispasmodic in asthma and hay fever.

Administration: Tablets—one or two tablets three times daily as directed by physician. Injection—one cc. daily or weekly as indicated.

Form Supplied: Tablets—bottles of 100 and 1,000; Injection—10-cc. multiple-dose vials.

Source: Testager & Co., Inc., Detroit, Mich.

UNITENSEN

Description: Aqueous parenteral solution, each cc. containing 2 mg. of cryptenamine.

Indications: For control of acute hypertensive states, preeclampsia, eclampsia, and preeclampsia with underlying essential hypertension.

Administration: As directed by physician.

Form Supplied: 5-cc. multiple-dose vials.

Source: Irwin, Neisler & Company, Decatur, Ill.

Other New Products

(Chemicals, clinical trial drugs, diagnostic aids, and equipment for the retail and hospital pharmacy, and new dosage forms of prescription products)

AQUA IVY A.P.

Aqua Ivy A.P., a new agent for either treatment or prevention of poison ivy dermatitis, is now being marketed by *Strong Cobb & Company, Inc.* Unlike most injectable drugs of this character, it is for the treatment as well as prophylaxis against poison ivy. For the first time, also, the injection material is in a

water solution. It is believed that the good results of the treatment of poison ivy dermatitis with Aqua Ivy A.P. are due entirely to that fact that the active drug antigen is an alum precipitate, and when it is injected into the tissues the slow continuous absorption provides a constant prolonged stimulating effect to the protection-creating mechanism of the body.

ASPIRIN, ORANGE FLAVORED ADULT, NORWICH

Norwich Pharmacal Company has recently introduced a new aspirin dosage for adults, Norwich Orange Flavored Adult Aspirin. It is a sweet orange-flavored aspirin of 5 gr. standard strength, and melts on the tongue—no water necessary.

BERUBIGEN—NEW DOSAGE FORM

A new dosage form of Berubigen has been recently announced by *The Upjohn Company*. Each cc. of the new product contains: vitamin B_{12} activity, 1,000 mcg.; benzyl alcohol, 15 mg.; and sodium chloride, 9 mg. It is supplied in 5-cc. vials.

CHLOROMYCETIN OTIC

Recently introduced on the market by *Parke, Davis & Company* is Chloromycetin Otic—a clear, colorless solution containing 0.5 per cent chloromycetin in propylene glycol with 1 per cent benzocaine added. The product is indicated for the treatment of acute and chronic infections of external and internal ear. It is supplied as a ready-mixed solution in 15-cc. bottles with dropper.

CHLOR-TRIMETON MALEATE CREAM 1%

Chlor-Trimeton Maleate Cream 1% is the *Schering Corporation's* newest addition to their line of Chlor-Trimeton products. Each Gm. contains 10 mg. chlorprophenpyridamine maleate [1-parachlorophenyl-1-(2-pyridyl)-3-dimethylaminopropane maleate]. It is supplied in 50-Gm. tubes, boxes of 12.

DILANTIN SUSPENSION

Dilantin Suspension is a specially designed preparation of Dilantin particularly adaptable to the treatment of children. It is indicated for the treatment of epilepsy, particularly grand mal or psychomotor seizures, and each teaspoonful (4 cc.) contains 100 mg. of Dilantin (diphenylhydantoin). It is supplied by *Parke, Davis & Company* in 8-oz. bottles.

ERYTHROCIN ORAL SUSPENSION, PEDIATRIC

Abbott Laboratories has recently introduced a new dosage form of Erythrocin (erythromycin stearate) called Pediatric Erythrocin Oral Suspension. Each teaspoonful (5 cc.) represents 100 mg. of Erythrocin. The recommended dosage is two to three mg./lb. (4.5 to 6.5 mg./Kg.) at four- to six-hour intervals. Thus, for a 50-pound child, one teaspoonful every four to six hours. The cinnamon-flavored liquid is supplied in 2-fl. oz. bottles, and will remain potent at least 18 months.

FURACIN NASAL WITH NEO-SYNEPHRINE

A new dosage form of Furacin-Nasal, called Furacin Nasal with Neo-Synephrine, has recently been announced by *Eaton Laboratories, Inc.* Having 0.02 per cent of the antibacterial agent Furacin (nitrofurazone) in a buffered aqueous solution, it also contains 0.25 per cent of Neo-Synephrine (phenylephrine). It is virtually free from central nervous stimulation. It is supplied in a ½ fl. oz. (15-cc.) bottle with a dropper.

GANTRICILLIN-300

Gantricillin-300—just introduced by *Hoffmann-LaRoche Inc.*—is a new and more potent dosage form of penicillin G potassium plus Gantrisin, for convenient oral therapy. Each scored tablet contains 300,000 units of crystalline penicillin G potassium together with 0.5 Gm. of Gantrisin. The tablets are available in bottles of 24, 100, and 500.

ILOTYCIN—NEW DOSAGE SIZE

A new convenient 200-mg. tablet of Ilotycin (erythromycin), which most nearly approximates the average adult dose, is now being marketed by *Eli Lilly and Company*. The new tablets are available in packages of 24 and 100.

INTRADERM TYROTHRICIN CREAM

As of October 1, 1953, *Wallace Laboratories, Inc.* are changing the name of their product Bactratycin Ointment to Intraderm Tyrothricin Cream. The Cream contains Tyrothricin U.S.P., 0.1 per cent, in Intraderm base and is indicated for pyogenic skin infections.

RONIACOL WITH AMINOPHYLLINE

Hoffmann-La Roche Inc. has just released a new product, Roniacol with Aminophylline, which provides a single, conveniently administered tablet that usually offers prompt yet sustained control of symptoms in vasospastic disorders. Each scored tablet contains 50 mg. of Roniacol and 100 mg. of aminophylline in a base containing magnesium trisilicate. The tablets are available in bottles of 100 and 500.

TRINSICON

A new wide-range hematinic, called Trinsicon (Hematinic Concentrate with Intrinsic Factor) has been recently announced by *Eli Lilly and Company*. A dosage of two pulvules a day provides full therapeutic requirements in the anemias. Trinsicon will be on the market within a few weeks.

4 in 1

AUREOMYCIN
TRIPLE SULFAS

TABLETS LEDERLE

for quick, sure action against

Gonorrhea
Bacillary Dysentery

A new combination drug, made only by Lederle. Four powerful antibacterial agents in one convenient form. The combined action is additive. This 4-in-1 drug provides rapid, effective action against gonococcal infections and bacillary dysentery. It is heavily detailed and advertised to physicians. Bottles of 12, 100 and 1,000.

FORMULA: Each tablet contains:

AUREOMYCIN HCl	125 MG.
SULFADIAZINE	167 MG.
SULFAMERAZINE	167 MG.
SULFAMETHAZINE	167 MG.

Lederle LEDERLE LABORATORIES DIVISION AMERICAN Cyanamid COMPANY 30 Rockefeller Plaza, New York 20, N.Y.

PUT AUREOMYCIN TRIPLE SULFAS ON YOUR "WANT" LIST NOW

PRESCRIPTION PRODUCTS

INDEX

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All items on which information has been received in the past thirty days are reported here. Manufacturers are urged to send details of their new products as early as possible, so that pharmacists, through these pages, will have full information at the same time, or even before, products are detailed to the physician. For inclusion in this free editorial department, send descriptive literature to the JOURNAL OF THE AMERICAN PHARMACEUTICAL ASSOCIATION, *2215 Constitution Avenue, N. W., Washington, D. C. Where possible, all descriptions should follow the style shown on these pages.*

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Geriatric Vitamin-Mineral Formula

GERIPLEX is favored by many physicians because it aids in the practice of preventive geriatrics. Each Kapseal contains essential mineral nutrients and eight important vitamins, plus the starch-digestant, Taka-Diastase,® and rutin.

Patients usually need one Kapseal daily as a supplement to the regular diet. During febrile illness, preoperative or post-operative periods, or whenever the possibility of vitamin deficiency threatens, dosage is adjusted by the physician as required.

Each GERIPLEX Kapseal contains:

Vitamin A	5000 units
Vitamin B_1 (thiamine hydrochloride)	5 mg.
Vitamin B_2 (G) (riboflavin)	5 mg.
Crystalline Vitamin B_{12}	2 mcg.
Nicotinamide (niacinamide)	15 mg.
Vitamin C (ascorbic acid)	50 mg.
Choline dihydrogen citrate	20 mg.
Mixed Tocopherols (vitamin E factors)	10 mg.
Taka-Diastase	1 gr.
Rutin	25 mg.
Ferrous sulfate	30 mg.
Copper sulfate	4 mg.
Manganese sulfate	4 mg.
Zinc sulfate	3 mg.
Dicalcium phosphate (anhydrous)	200 mg.

GERIPLEX Kapseals (No. 382) are supplied in bottles of 100 and 500.

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DETROIT, MICHIGAN

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Cortef*

for topical anti-inflammatory therapy of dermatitis

A completely new approach to the management of dermatitis has been achieved. Upjohn scientists have developed Cortef Acetate Ointment for the application of the most active adrenal steroid —compound F—into affected skin layers.

Up to now, the conventional treatment of dermatitis has been primarily empirical and symptomatic (e.g., calamine for pruritus). Cortef Acetate Ointment offers a new approach through its anti-inflammatory effect. It permits the full utilization of the anti-inflammatory activity of compound F (hydrocortisone) at the tissue level without producing systemic effects.

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acetate ointment* Upjohn

(BRAND OF HYDROCORTISONE ACETATE)

SUPPLIED:

Cortef Acetate Ointment is available in 5 Gm. tubes in two strengths—2.5% concentration (25 mg. per Gm.) for initial therapy in more serious cases of dermatitis, and 1.0% concentration (10 mg. per Gm.) for milder cases and for maintenance therapy.

ADMINISTERED:

A small amount is rubbed gently into the involved area one to three times a day until definite evidence of improvement is observed. The frequency of application may then be reduced to once a day or less, depending upon the results obtained.

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- **Very stable in dry form. Water is added to the dry powder when it is dispensed; in this form it is stable for two weeks even when kept at *room temperature*.**

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Also available:
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Lilly

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